Patterns of cannabis use in first-episode psychosis

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Abstract

There is ample evidence that patients with psychosis are more likely to use illicit substances than the general population, with cannabis being the most popular. Research has also shown that cannabis use is associated with poor prognostic outcomes in patients with an established psychotic disorder. It is important to understand the reasons patients with psychosis endorse for their cannabis use and findings so far point towards an 'alleviation of dysphoria' model rather than the 'self-medication' hypothesis. It is not known how the level of motivation to change cannabis use can affect patients' actual use. Lack of validated readiness to change questionnaires for use with psychotic populations makes it essential to develop and validate such measures.

The aim of this thesis was to evaluate the reasons for cannabis use and its effects on psychotic outcomes in a patient cohort with first-episode psychosis. The association between cannabis use and other illicit drug use was also investigated. Readiness to change was evaluated as a predictor of cannabis use outcomes using two questionnaires.

The main finding was that cannabis use was not associated with psychotic outcomes but was related to other illicit drug use. With regards to reasons, patients chose enhancement and social motives as most important for their cannabis use providing support for the 'alleviation of dysphoria' model. Preliminary analysis showed no clear pattern of association between readiness to change and cannabis use outcome. Utility of two readiness to change measures for use with patients with psychosis was not validated.

These findings add to the small evidence base that cannabis use is not associated with prognostic outcomes in psychosis. No evidence for the self-medication hypothesis was observed. Readiness to change was not associated with cannabis use outcomes signifying the need for using validated measures to assess motivation in psychotic populations.

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Chapter 1 – General Introduction

1.1 Aims of the chapter

The aims of this chapter are to provide:

1. A brief description of the current understanding of psychosis, its aetiology and prognosis and a definition of the nature of first-episode psychosis for this thesis.
2. A brief history and description of cannabis, its role in the aetiology of psychosis and its prevalence in, and effects on, psychotic disorders.
3. The rationale for exploring reasons for cannabis use, a description of proposed models for co-morbid substance use and psychiatric disorders and a summary of the self-reported reasons for substance use in psychiatric patients.
4. The rationale for investigating readiness to change cannabis use, an overview of the literature on readiness to change substance use in co-morbid psychiatric populations and a description of the most commonly used assessment tools.
5. A description of the thesis aims.
6. An outline of the thesis.

1.2 Psychosis

1.2.1 Introduction

Psychosis, translated from the Greek as 'abnormality of the mind and soul', is a broad concept that comprises a number of disorders (Ross, 2005). From the introduction of the concept of psychosis in 1841 by Canstatt (Burgy, 2008), who used it synonymously with 'psychic neurosis' to the present day of manual classifications and diagnostic instruments, the experience of psychosis has remained fairly constant. Psychosis is often associated with a loss of touch with reality and manifested as hallucinations, delusions and thought disorder (DSM-IV, American Psychiatric Association, 1994). In the current version of the International Classification of Diseases (ICD-10, World Health Organization [WHO], 1992), a number of diagnoses are grouped underneath the wider term of psychosis: schizophrenia, schizotypal disorder, persistent delusional disorders,

acute and transient psychotic disorders, induced delusional disorder, schizoaffective disorders, other non-organic psychotic disorders and unspecified non-organic psychosis.

For the purposes of this thesis, 'first-episode psychosis' will be defined as a first experience of one or more psychotic symptoms for a minimum of 7 days and will include patients from all the aforementioned categories as well as those with bipolar and substance-use disorder with psychotic symptoms. While there are differences between categories, research on broad psychosis has the advantage of exploring characteristics of the wider diagnostic group, which would have been otherwise missed if one or more categories were omitted.

Estimates of incidence and prevalence of psychosis tend to vary between reports. It is estimated that the prevalence of all clinically important psychotic disorders in the general population is around 3% (van Os, 2009). Lifetime prevalence rates of schizophrenia have been reported between 0.4% (Saha et al, 2005) and 0.9% (Perälä et al, 2007) while the ratio of male to female diagnosed schizophrenia is about 1.4:1 (McGrath et al, 2008).

1.2.2 Aetiology of schizophrenia

Schizophrenia is subject to a major genetic influence. The risk is about 6.5% in first-degree relatives (Kendler et al, 1993) and rises to more than 40% in the co-twins of monozygotic twins with schizophrenia (Cardno et al, 1999). Twin studies suggest that heritability is around 80% (Cardno et al, 1999) though such heritability measures include not only the effect of genes but also of gene-environment interaction (van Os et al, 2008).

A large number of studies have examined the relationship between various environmental events and the onset of schizophrenia. The best replicated include early hazards to the brain such as obstetric complications (Cannon et al, 2002a). In adulthood, environmental stressors including migration, urban life and social isolation have been shown to further increase the risk (Boydell et al, 2004).

Kapur et al (2005) proposed that the excessive release of dopamine in acute psychosis leads to increased attention and importance (salience) being attributed to neutral everyday experiences and events. In turn, delusions arise

from an attempt by the patient to explain the unusual salience of environmental stimuli.

Although the dopamine system does not appear to be implicated in the origins of schizophrenia, it has been proposed that the influence of the above genetic and environmental risk factors can leave an individual more vulnerable to dopamine dysregulation, which in turn acts as a final common pathway to the development of psychosis (Di Forti et al, 2007).

1.2.3 Prognosis

Psychosis is often viewed as a condition with fairly poor prognosis and outcome. A systematic review of patients in their first episode of psychosis by Menezes et al (2006) surprisingly observed that only 27% of the sample showed a poor outcome, with 42% showing a good outcome. Most patients have been reported to experience some level of recovery with only a small proportion remaining completely symptom-free (Wunderink et al, 2009). Poor outcome (e.g. increased symptoms, hospital readmissions, absence of remission) can be exacerbated by longer duration of untreated psychosis, reduced pre-morbid functioning, gradual onset of the disease and low insight. Schizophrenia is also associated with high mortality rates from increased risk of suicide (Mortensen and Juel, 1993), co-morbid physical health problems (Leucht et al, 2007) and accidents and trauma (Saha et al, 2007). In summary, psychosis and particularly schizophrenia are associated with adverse outcomes both in terms of mental as well as physical health.

1.3 Cannabis

1.3.1 Introduction

Although historically most attention has focused on the use of amphetamine and methamphetamine, which can produce a schizophrenia-like picture (Paparelli et al, 2011), cannabis is currently the most frequently used illicit substance in the world (United Nations Office on Drugs and Crime, 2010). It is obtained from the Cannabis Sativa plant. There are over 400 natural components found within this plant of which around 60 have been classified as 'cannabinoids'. Delta-9 tetrahydrocannabinol (Δ^9-THC/ THC) is the primary

psychoactive constituent of cannabis but another important cannabinoid is cannabidiol (CBD), which appears to counteract some of the psychoactive effects of THC (Zuardi et al, 2006). The varieties of cannabis typically available are marijuana or grass, resin or hash and most recently sinsemilla or skunk. Marijuana or grass, the herb varieties, are derived from the flowers and leaves of the plant; resin or hash are derived from the secretions during the flowering process and sinsemilla or skunk comes from the female plant at its seedless stage.

A report by the London Metropolitan Police revealed the different levels of component chemicals in each of the varieties. Samples seized and analysed showed that marijuana and hash on average contained 2-4% of Δ^9-THC compared to around 14% found in skunk. It was also observed that very low concentrations of CBD were present in the grass variety and almost completely absent in skunk – an alarming finding considering the increasing popularity of skunk and the lack of potentially protective components (Potter et al, 2008).

1.3.2 Brief history of cannabis

Although use of cannabis as either a medicinal product or recreational drug was fairly uncommon in the U.K. until the 1950s, it has been documented copiously around the world since the 16th century. At that time most information on cannabis (or hemp) came from observations of doctors accompanying empire-builders into India and, uninterested yet in its psychoactive properties, they were more excited about its potential as a source of rope and string. By the 18th century, British travellers returning from Asia were eager to share their stories of this unique substance and by the 19th century the empire had expanded sufficiently to allow systematic attention to focus on cannabis by scientists and doctors. William Brooke O'Shaughnessy was one of the first scientists to conduct a range of experiments with cannabis and reportedly cure a range of conditions including rheumatism, rabies, tetanus and cholera. While interest was growing in the medical effects and potential benefits of cannabis, the British in India finding themselves amongst the largest market for cannabis taxed the cannabis trade. Producers who evaded laws and regulations were penalized and so started cannabis being associated with criminality (Mills, 2003).

Throughout the 19th century, British doctors continued to regard cannabis as a valuable medicine and it was evidence from India that first pointed to a relationship between cannabis and insanity. By the late 1800s the Indian Hemp Drugs Commission (IHDC) was established to investigate these claims in the colonies and its report comprises one of the most complete surveys on cannabis use to this day. They discarded any association between cannabis use and social problems and reported that moderate or habitual use would not cause any adverse health effects (Mills, 2003).

At the dawn of the 20th century while cannabis was still widely consumed in India and the British were still acquiring income from ongoing taxation, the drug remained largely unknown in the UK besides to a small party of doctors, scientists and an 'elite' artistic group. It wasn't until the 1920s with the commission of the League of Nations Advisory Council on Opium and two opium conferences in 1924-1925, that the Coca Leaves and Indian Hemp Regulations of 1928 saw a set of restrictions on cannabis imposed for the first time by British law (Mills, 2003).

This law was applied rather erratically until the Misuse of Drugs Act in 1971, which introduced the drug classification system and penalty guidelines assigning cannabis a class B grouping. This remained until 2004 when, in accordance with recommendations from the Advisory Council on the Misuse of Drugs (ACMD), it was downgraded to class C. In 2009, against ACMD advice, it was upgraded and returned to class B.

Even from the early days of hemp trade and experimentation, laws and policies have defended and challenged positions on cannabis continuously. As the most popular illicit drug around the world, which occasionally benefits from regulation such as in the Netherlands and more recently Portugal as well as being prescribed for medicinal purposes in the United States, the debate on its effects and safety is ongoing.

1.3.3 Prevalence of cannabis and other drug use in schizophrenia and first episode psychosis

Patients with severe mental illness have high rates of substance use disorder (Regier et al, 1990; Mueser et al, 1995; McCreadie, 2002). Hambrecht and Häfner (1996) found that, in patients with a first admission of schizophrenia, the

rates of substance use were twice as high as in healthy controls. Similarly high rates have been also documented in patients with a first episode of psychosis (FEP). High rates of substance misuse were also found by Addington and Addington (2007) in a study of admissions to an early-psychosis programme. Barnett et al (2007) found that substance use among people with a FEP was twice that of the general population with poly-drug abuse being common. Lifetime prevalence of substance use in patients with FEP has been reported as high as 74% (Lambert et al, 2005) and as low as 23% (Sevy et al 2001). Some of this variability will naturally be due to methodological differences but it probably also reflects differences in drug availability and price and the cultural acceptability of drug use in the different settings.

Many studies have drawn attention to the high levels of cannabis consumption by patients with psychosis. For example, Green et al (2005) analysed 53 treatment studies and 5 epidemiological studies and reported that on average 42% of psychotic patients had used cannabis in their life. Lifetime use of cannabis in the general population is lower; for example, around 30% in the UK (Home Office, 2009/2010).

In light of the high prevalence of cannabis use among young people, a lot of research has focused on its use in FEP (Kavanagh et al, 2004). Sevy et al (2001) found that cannabis was the most popular illicit substance in a sample of patients presenting with a first episode of schizophrenia or schizoaffective disorder. Barnett et al (2007) noted that cannabis abuse was reported by 51% of patients; use in the last month by patients was more than twice as high as in the general population (29% vs 12%). In another study, 63% of individuals with first-episode schizophrenia had at some time used cannabis and 32% were current users (Harrison et al, 2007). Furthermore, Linszen et al (1994) reported that 26% of recent-onset schizophrenic patients were abusing cannabis.

1.3.4 Role of cannabis in aetiology of schizophrenia

Experimental studies investigating the acute effects of cannabis intoxication have shown that it can induce transient psychotic symptoms in healthy individuals and worsen symptoms in those with an already established psychotic illness. D'Souza et al (2005) administered intravenous Δ^9-THC to 13 patients with clinically stable schizophrenia or schizoaffective disorder. Δ^9-THC

significantly increased positive, negative and general schizophrenia symptoms. In addition, patients were more vulnerable to the effects of Δ^9-THC compared to healthy controls (D'Souza et al, 2004). THC impaired learning and recall in a dose-dependent manner. Further evidence comes from Morrison et al (2009), who conducted a study in which 22 healthy males received intravenous THC or placebo in a double-blind fashion. Administration of THC induced positive psychotic symptoms, anxiety and dysphoria. There was also marked impairment on working and episodic memory and executive function.

Although these studies demonstrate the short-term effects of cannabis intoxication, they cannot identify any causal relationship between cannabis and chronic psychosis. Evidence for an association between cannabis use and the development of schizophrenia has been demonstrated through longitudinal studies. The first such study followed up a cohort of 50,087 Swedish conscripts (Andreasson et al, 1987). Those who had smoked cannabis at least once by age 18 were twice more likely to develop schizophrenia in the following 15 years than non-users. The risk increased in a dose-dependent fashion to 6-fold for those who had used cannabis more than 50 times. After controlling for 11 variables the risk remained significant even if somewhat lower. Similar findings were reported in a follow-up of this cohort after 27 years (Zammit et al, 2002).

Another study, in the Netherlands, investigated the effects of cannabis use on self-reported psychotic symptoms in 4,045 psychosis-free individuals at baseline and then 12 and 36 months later (van Os et al, 2002). There was a dose-response relationship between baseline cannabis use and psychotic symptoms at follow-up, with users being almost twice as likely to report psychotic symptoms and around 3 times more likely to develop a needs-based diagnosis of psychotic disorder than non-users after adjusting for confounders.

In the Netherlands, Henquet et al (2005) carried out a study with 2,437 young people. Cannabis use in adolescence and young adulthood increased the risk of psychotic symptoms in later life. Cannabis use at baseline was associated with an almost double risk of developing psychotic symptoms four years later even after adjusting for a number of social confounders and other drug use; this relationship was again dose-response dependent with increasing frequency of cannabis use.

Arseneault et al (2002), in the Dunedin Birth Cohort Study in New Zealand, followed up a cohort by collecting information on psychotic symptoms at age 11, on drug use at age 15 and 18 and on psychotic symptoms at age 26. People who had used cannabis by age 15 were 4 times more likely to have a diagnosis of schizophreniform disorder at age 26 than controls. After controlling for psychotic symptoms at age 11, the risk for schizophreniform disorder was not statistically significant but remained higher in those who used cannabis at age 15. There was no significant risk associated with developing schizophreniform disorder and cannabis use by age 18. Combined findings from age 15 and age 18 analyses showed an increased risk for schizophreniform disorder at age 26, which only slightly decreased after controlling for confounders. Also in New Zealand, the Christchurch study followed participants for more than 20 years and found that young people using cannabis by age 18 had an almost 2-fold risk of developing psychotic symptoms. This association again increased in a dose-response manner and remained significant after controlling for confounders (Fergusson et al, 2005).

Most recently, McGrath et al (2010) assessed cannabis use retrospectively in an Australian birth cohort study of 3,801 young adults at 21-year follow-up. Those who had smoked cannabis for 6 or more years were 4 times more likely to score highly on the Peters et al (1999) Delusions Inventory and twice as likely to develop non-affective psychosis compared to those who had never used cannabis. The former association was still evident when 228 sibling pairs were compared. Furthermore, the authors found that a greater length of time since first use of cannabis and more frequent use of cannabis at follow-up were associated with early-onset hallucinations.

Table 1.1 gives a summary of 11 longitudinal studies conducted in the general population investigating cannabis use and the risk of developing a psychotic disorder.

Table 1.1 Summary of longitudinal studies investigating cannabis use and risk of psychotic disorders

Study and country of origin	Design	Sample size	Length of follow-up period	Odds Ratio (adjusted; 95% CI)
Andreasson et al, 1987; Zammit et al, 2002); Sweden	Cohort (conscripts)	50, 053	15 years and 27 years respectively	2.3 (1.0-5.3) and 3.1 (1.7-5.5) respectively
Tien & Anthony (1990); USA	Population based	4,494	No follow-up	2.4 (1.2-7.1)
Arsenault et al, (2002); New Zealand	Cohort (birth)	1,034	15 years	3.1 (0.7-13.3)
van Os et al (2002); The Netherlands	Population based	4,045	3 years	2.8 (1.2-6.5)
Weiser et al (2002); Israel	Population based	9,724	4-12 years	2.0 (1.3-3.1)
Fergusson et al (2005); New Zealand	Cohort (birth)	1,265	3 years	1.8 (1.2-2.6)
Stefanis et al (2004); Greece	Cohort (birth)	3,500	No follow-up	4.3 (1.0-17.9)
Ferdinand et al (2005); Netherlands	Population based	1,580	14 years	2.8 (1.79-4.43)
Henquet et al (2005); Netherlands	Population based	2,437	4 years	1.7 (1.1-1.5)

Table 1.1 Summary of longitudinal studies investigating cannabis use and risk of psychotic disorders (cont.)

Study and country of origin	Design	Sample size	Length of follow-up period	Odds Ratio (adjusted; 95% CI)
Wiles et al (2006); UK	Population based	8,580	18 months	1.5 (0.55-3.94)
McGrath et al (2010); Australia	Cohort (birth)	3,801	21 years	2.1 (1.002- 4.3)

Finally, Di Forti et al (2009) found that patients presenting with a first episode of psychosis in south London were 6 times more likely to have smoked 'skunk' than a comparative sample of the general population. These authors concluded that the risk of psychosis increased with the frequency and length of cannabis consumption and the potency of the preparation used. Modern forms of cannabis could be potentially more harmful and with the relative decrease of cannabidiol concentrations in skunk some protective effects may have been removed making this a more potent form of the drug.

1.3.5 Effects of cannabis use on established psychotic disorders

Persistent substance use by those already psychotic has been associated with increased suicidal ideation (Hawton et al, 2005), more positive symptoms (Pencer and Addington, 2003) and risk of illness and injury (Dickey et al, 2000). 'Revolving door' admissions occur at almost twice the frequency for users than non-users (Menezes et al, 1996) and admissions by substance users are also reported to be lengthier and more severe. Patients with psychosis who abuse drugs are also less likely to adhere to treatment (Janssen et al, 2006) and more likely to suffer from stress (Barrowclough et al, 2005) and social exclusion (Todd et al, 2004).

Cannabis use appears to play a role in causing or increasing problems among patients with established psychosis (Mueser et al, 2000). A follow-up study of psychotic patients with persistent cannabis use found that they were at

risk of increased symptoms, hospital readmissions, and absence of remission (Sorbara et al, 2003). Grech et al (2005) also found that persistent cannabis use led to a more continuous illness at follow-up. Continuous cannabis use also made patients more likely to relapse (Linszen et al, 1994) and to suffer from problems leading to increased violence and criminal behaviour (Miles et al, 2003). A systematic review also showed that persistent use by patients with psychosis was consistently associated with increased relapse and non-adherence to treatment (Zammit et al, 2008).

It is still unclear to what extent cannabis use can affect patients' physical health. Based on the evidence for the appetite-enhancing effects of this drug, as shown in animal studies and research with cancer patients (Nelson et al, 1994; Hao et al, 2000), cannabis use may lead to weight gain. Isaac et al (2005) found that patients who reported cannabis use at admission had higher blood glucose levels and greater weight gain at 6 weeks than non-smokers. Further research needs to be conducted with larger populations, longer follow-ups and a focus on the interaction between cannabis use, antipsychotic properties and general lifestyle (i.e. diet, exercise), which can independently affect weight fluctuations. Finally, concerns have been expressed about the respiratory effects of cannabis, which is traditionally smoked mixed with tobacco and can potentially introduce further risks for tobacco-related illness, such as lung cancer (Hashibe et al, 2005).

1.4 Reasons for cannabis use

1.4.1 Introduction

Studies have shown that patients with psychosis are more likely to use illicit drugs than the general population, with cannabis being the most popular. As we have seen, there exists evidence that cannabis use can contribute to the onset of schizophrenia and poor outcome in patients with established psychosis. Therefore, understanding why patients use cannabis is important. If cannabis-using behaviour and its correlates are different for patients with psychosis, treatment may have to adapt in meeting these special needs. Before assessing the specific reasons for cannabis use, an overview of the theories of co-morbid substance misuse and psychotic illness as well as a summary of the existing

literature on reasons for general substance use in psychiatric populations will be presented.

1.4.2. Models and theories explaining co-morbid substance misuse and psychotic illness

A variety of models have been proposed to explain co-existing substance misuse and psychosis (Mueser et al, 1998):

Secondary substance use disorder models: These postulate that substance-use disorders are secondary to, and therefore are caused by, severe mental illness.

a) The self-medication hypothesis*:* The most widely cited is the "Self Medication Hypothesis" (Khantzian, 1985, 1997) which theorises that patients take specific substances to relieve particular symptoms; substances are not chosen at random but have "psychopharmacological specificity." Khantzian (1997) also argued that patients with schizophrenia may start taking substances to self-medicate prodromal symptoms, prior to the onset of the disorder, and that heightened rates of stimulant use in this population may be an indication of patients' attempt to self-medicate negative symptoms. Self-medication of symptoms caused by antipsychotic medication may also be occurring (Schneier and Siris, 1987). Mueser et al (1998) argued that the validity of the self-medication hypothesis depends on the existence of the following relationships: patients will report using certain substances to relieve particular psychiatric symptoms; each psychiatric diagnosis will be associated with the use of particular substances in epidemiological studies; observational studies will show that patients use specific substances to change symptoms characteristic of their psychiatric disorder. Mueser et al (1998) consider that the available evidence does not currently support any of these relationships.

b) Alleviation of dysphoria model*:* A variation of the traditional self-medication hypothesis proposes that substance misuse occurs to alleviate dysphoric experiences such as boredom, depression and loneliness to which patients with severe mental illness may be particularly susceptible. This model assumes that patients may engage in poly-substance misuse and do not choose specific substances to medicate specific undesired psychological states.

Secondary psychiatric illness model: This model assumes that substance-misuse disorders can cause psychiatric disorders (e.g. drug-induced psychosis).

Common factor model: This model proposes that psychiatric and substance-use disorders frequently co-occur due to underpinning shared biological, psychological or social factors such as genetics, family history, antisocial personality disorder, childhood trauma, cognitive impairment or lower socioeconomic status. Gregg et al (2007) argue that it is unlikely that one factor will be the cause of co-morbidity but rather a combination of multiple-risk factors.

Bi-directional models: This model assumes that the psychiatric disorder and substance misuse activate and perpetuate each other with substance misuse acting as a stressor in biologically vulnerable individuals who are especially sensitive to small amounts of substances.

Multiple risk factor models: An affect-regulation model proposed by Blanchard et al (2000) suggests that patients with schizophrenia use substances to cope with negative affect. According to the model, trait rather than state factors, such as neuroticism (which is associated with negative affective states) and impulsivity (which is associated with pleasure seeking and risk taking) interact with stress and make substance use more likely (Hides et al, 2004).

According to the social learning theory (Bandura, 1977), drug use is viewed as a strategy adopted by people who have positive beliefs about its effects and limited coping skills. Furthermore, Barrowclough et al's model of maintenance of substance use in psychosis (Barrowclough et al, 2007), adapted from Marlatt and Gordon's model of addiction (Marlatt and Gordon, 1985), postulates that certain environments and cues may lead patients to use substances. The same environments and cues may have a connection to psychotic symptoms or negative experiences related to psychosis. In the context of poor problem-solving skills and coping strategies and lack of other sources of pleasure, the perceived benefits of substance use become positively reinforced. However, this behaviour may cause patients to feel worse leading to further substance use. A problematic cycle ensues whereby substance use continues and psychotic symptoms persist. The availability of drugs and acceptability of use among peers combined with the learned positive benefits of drug use also feed

into the cycle. "External stressors", such as problems with family members, may lead to more distress and substance use causing worsening of psychotic symptoms.

Finally, a cognitive-behavioural bi-directional account of substance abuse (Hayes et al, 1996: pp 1154) describes the abuse as a consequence of "experiential avoidance [which is] a.....psychological process.....that occurs when a person is unwilling to remain in contact with particular private experiences (e.g. bodily sensations, emotions, thoughts, memories, behavioural predispositions) and takes steps to alter the form or frequency of these events and the contexts that occasion them." Thus, substance misuse acts as a short-term strategy to change these private emotional states (Parrott, 2008).

Despite the multi-factorial and holistic approach these models take in regards to co-morbidity, there is little empirical evidence to suggest that any one applies to all patients. It may be that different models may be more appropriate for different groups of patients and on an individual level more than one model may be valid.

1.4.3 The self-report literature on reasons for substance use among psychiatric patients

A number of studies have investigated self-reported reasons for general illicit substance use in psychiatric patients. An analysis of interviews with 19 patients with recent onset psychosis, who used cannabis and/or other substances, identified four main themes influencing their use (Lobbana et al, 2010). One theme was the "influence of perceived drug norms on behaviour", which encompassed the acceptability of drug use in patients' communities or the act of purposefully not conforming to social norms. The second theme was "attributions for initial and ongoing drug-taking behaviour", where some patients attributed taking drugs to internal reasons (e.g. it was a personal choice) and others attributed it to external factors (e.g. belonging to a social group). The third theme was "changes in life goals affecting drug use" such as employment, the increased importance of good health, maintaining relationships and income. "Beliefs about links between mental health and drug use" was the final theme, which yielded different views among patients. Some patients

reported using substances as a coping mechanism for their mental health problems, while others acknowledged a predisposition to mental health problems, which their substance use may have triggered. Some patients said that substance use exacerbated their symptoms and problems, whereas others did not acknowledge any relationship between substance use and their mental illness.

Table 1.2 lists the studies, which have assessed the reasons psychiatric patients give for using substances in general. The reasons have been categorized according to Spencer et al's (2002) modification of the Drinking Motives Questionnaire (Cooper, 1994).

Table 1.2 Reasons for general substance use among psychiatric patients

Author Country Year	Assessment measures	Sample characteristics (size, diagnosis)	REASONS FOR USE (SUBSTANCE USE IN GENERAL)				
			Enhancement, intoxication	**Social effects, conformity/ acceptance**	**Coping with positive symptoms**	**Coping with dysphoria and negative symptoms**	**Coping with medication side effects**
Laudet et al USA 2004	Interview	310 patients with a variety of self-reported diagnoses	10%- fun/experiment/curiosity 2%- wanted to drink/use	58%- to fit in with peers 12%- family member/ caretaker used 9%- problems at home or school 4%- traumatic/ stressful event	Not reported	12%- emotional/ mental issues	Not reported

Table 1.2 Reasons for general substance use among psychiatric patients (cont.)

Author Country Year	Assessment measures	Sample characteristics (size, diagnosis)	REASONS FOR USE (SUBSTANCE USE IN GENERAL)				
			Enhancement, intoxication	**Social effects, conformity/ acceptance**	**Coping with positive symptoms**	**Coping with dysphoria and negative symptoms**	**Coping with medication side effects**
Test et al USA 1989	Interview	27 patients diagnosed with psychotic disorders	11%- to have more energy 7%- to stay awake 7% to feel better physically	44%- something to do with friends 4%- to be more likable	7%- decrease hallucinations	63%- relieve boredom 44%- to feel less anxious/ more relaxed 41%- aid sleep 15%- relieve pain 15%- to feel good about oneself 7%- to feel normal	18.5%- to make side effects more tolerable

Table 1.2 Reasons for general substance use among psychiatric patients (cont.)

Author Country Year	Assessment measures	Sample characteristics (size, diagnosis)	REASONS FOR USE (SUBSTANCE USE IN GENERAL)				
			Enhancement, intoxication	**Social effects, conformity/ acceptance**	**Coping with positive symptoms**	**Coping with dysphoria and negative symptoms**	**Coping with medication side effects**
Dixon et al USA 1991	Interview	53 patients diagnosed with psychotic disorders	38%- to get high 33%- to increase pleasure 30%- to increase energy 26&- to increase emotions 24%- to talk more 21%- to be more creative 11%- to satisfy curiosity 10%- to increase concentration	29%- to go along with the group 9%- to work and study better	6%- to decrease hallucinations 3%- to decrease suspiciousness	38%- to decrease depression 34%- to relax	8%- to decrease side effects of medication

Table 1.2 Reasons for general substance use among psychiatric patients (cont.)

Author Country Year	Assessment measures	Sample characteristics (size, diagnosis)	REASONS FOR USE (SUBSTANCE USE IN GENERAL)				
			Enhancement, intoxication	**Social effects, conformity/ acceptance**	**Coping with positive symptoms**	**Coping with dysphoria and negative symptoms**	**Coping with medication side effects**
Gregg et al UK 2009 (10 most popular reasons for use given only)	Q methodology	45 patients diagnosed with psychotic disorders	73%- to feel good/have a laugh/ be happier 71%- when feeling confident or relaxed 69%- celebration	84%- to have a good time with friends	Not in top 10 reasons	91%- to chill out or relax 80%- relieve boredom 78%- to aid sleep 78%- when feeling stressed 76%- escape from problems and worries 73%- relieve anxiety/tension	Not in top 10 reasons

Spencer et al (2002) assessed motivations for cannabis and alcohol use in 69 patients with psychotic disorders from Australian psychiatric wards and clinics. Patients mainly reported taking these substances for enhancement, social and conformity reasons and to cope with dysphoric experiences- motives similar to those of people who misuse substances in the general population (Cooper, 1994). The authors also report a possible additional motive - relief of positive symptoms and side effects, although patients rarely rated this as their motive for use. These subgroups of patients were established on the basis of both cannabis and alcohol use and conclusions regarding subgroups cannot be drawn for specific substances.

Laudet et al (2004) investigated why patients, with a variety of diagnoses, attending a self-help group in the USA first started using substances. Over half of the patients reported wanting to fit in with peers as the main reason for initiating use. Test et al (1989) looked at reasons for substance use among patients with schizophrenia or schizophrenia-related disorders. The majority said they used substances to relieve boredom followed by using as a social activity and to feel less anxious and more relaxed. Almost half reported that they used substances for sleep difficulties.

Dixon et al (1991) investigated reasons for substance abuse among patients diagnosed with schizophrenia and substance abuse/ dependence. Most reported using substances to get high and reduce feelings of depression followed closely by using substances to relax and to increase feelings of pleasure. The authors reported that reasons for use did not differ substantially between different drugs.

Recently, Gregg and colleagues (2009) recruited patients with schizophrenia and schizoaffective disorder with co-morbid alcohol or substance abuse/ dependence. Almost all patients reported using substances to "chill out or relax." Social reasons were also very important followed by relief of boredom. The following groups emerged through a factor analysis: those who use substances for social and enhancement reasons, those who use for self-medication and those who take substances to change their perception of experiences.

In summary, findings from the aforementioned studies suggest that psychiatric patients choose substances for their mood-enhancing properties and social effects with a small minority endorsing self-medication motives (relief of positive symptoms and medication side effects) for their substance use.

1.5 Readiness to change cannabis use

1.5.1 Introduction

Despite strong evidence for damaging effects that persistent cannabis use can have on psychotic patients, many fail to gain from substance use treatment due to lack of motivation and drop-out (Drake et al., 2004). Motivation is crucial in determining why and how people change problematic health behaviours (Miller, 1985), including those patients with dual diagnosis (Pantalon and Swanson, 2003). The concept incorporates concerns about the behavior and need for change, willingness to take responsibility, making a commitment and sustaining the behaviour change (Miller and Rollnick, 2002). Readiness to Change (RTC) refers to the degree to which an individual is motivated to change a problematic behaviour and includes 'initial attitudinal shifts reflecting dissatisfaction with a behaviour or lifestyle, receptivity to discussing problematic aspects of the behaviour, initial modifications and ongoing change efforts until a new behaviour or lifestyle is established' (Carey et al, 1999a; pp 245).

Although readiness to change in substance users has been well researched, this concept has only recently begun to be explored in patients with co-occurring severe mental illness and substance use disorders (Ziedonis and Trudeau, 1997; Zhang et al, 2004). A summary of research that has examined readiness to change substance-using behavior in patients with co-morbid psychiatric and substance use disorders as well as an overview of the most common RTC assessment instruments will be provided.

1.5.2 Readiness to change substance use in co-morbid populations

Carey et al (2002) found that patients who were prepared for change reported higher problem recognition, steps taken toward change, cons of using, and benefits of quitting. Active change also meant less frequent substance use

and lower perceived costs of quitting. In another study, higher motivation on a 5-point Likert scale at baseline or discharge was associated with increased rates of abstinence at 1-month follow-up (Ries and Ellingson, 1990).

Zhang et al (2006) found that, in patients with severe and persistent mental health illness, taking increasing steps to reduce alcohol use led to lower alcohol use in that period and significant decrease in alcohol use over time. Moreover, Velasquez et al (1999) found that severe alcohol use in dually diagnosed patients at pre-treatment was related to higher readiness to change. Pantalon et al (2002) also found that more severe alcohol and cocaine problems at baseline were related to higher readiness to change.

In contrast, the relationship between readiness to change and involvement in treatment has not been straightforward. Ziedonis and Trudeau (1997) expected that treatment seekers would have higher motivation to change their drug use but found that patients with high motivation were not enrolled in treatment. Similarly, Pantalon and Swanson (2003) found that patients with lower motivation to change were more treatment-adherent than patients with higher motivation.

There are several possible reasons for these contradictory findings. Firstly, as most of the research has included patients with schizophrenia, it is possible that the presence of psychotic symptoms may have obscured any relationship. Negative symptoms in particular, such as avolition and anhedonia, can hinder the measurement of motivational concepts of readiness to change, as patients might not be able to apply the effort needed to complete such demanding measures (Carey et al, 2001). Secondly, a variety of instruments were used to assess motivation in different studies. Thirdly, patients with schizophrenia display deficits in a number of cognitive areas including executive function, memory, language and attention (Kuperberg and Heckers, 2000; Bellack et al, 1999; Buchanan et al, 2005). Lack of self-awareness and difficulties with abstract thinking could impede patients' ability to express intention for behavioural change (Carey et al, 2001).

It would not be surprising if patients suffering from both schizophrenia and substance use were at a cognitive disadvantage to patients with only one of

the two disorders (Tracy et al, 1995). However, research in the area has shown that patients with psychosis who use substances perform better on cognitive tests, such as non-verbal functioning, than those patients who have never used drugs (Carey et al, 2003; Potvin et al 2005: McCleery et al, 2006). This may be because those who became psychotic following drug abuse have less developmental impairment than other schizophrenic patients.

Of course, the role of motivation and RTC in dual diagnosis populations can only be addressed appropriately if we implement accurate and valid measures and a number of instruments based on the Transtheoretical Model of change (TTM; Prochaska and DiClemente, 1983) have been developed to measure motivation to change among drug users. The TTM proposes 5 stages of change to signify the continuous and recurring process by which people change addictive behaviours: pre-contemplation, contemplation, preparation, action and maintenance. The TTM has, in recent years, received criticism with regards to its validity and applicability. Authors have argued that the TTM provides a descriptive rather than evaluative means of understanding addictive behaviour (Sutton, 2001) and it oversimplifies the process of change, since it creates arbitrary categories related to arbitrary definitions (Littel and Girvin, 2002). Taking this into account, the TTM provides a detailed characterization of intentional behaviour change and recommends matching the proposed interventions to the respective stage of change. As the stage must be identified (Vilela et al, 2009), a number of instruments have been designed for that purpose and are reviewed below.

1.5.3 Instruments for assessment of readiness to change

Staging Algorithms

The most common instruments are the staging algorithms designed to assign individuals to the stages of change based on their response to 4 or 5 questions (Carey et al, 1999a). They are quick and easy to complete and can be adapted for different populations and substances. Initially developed for smoking cessation (Prochaska et al, 1994), their effectiveness in assessing RTC for other substances has not yet been determined. Algorithms have also been

criticized for the subjective manner in which stages are defined and how previous behaviours are used to predict readiness to engage in a similar behaviour in the future (Carey et al, 1999a).

Self-report questionnaires

One of the most commonly used questionnaires is the University of Rhode Island Change Assessment (URICA; DiClemente & Hughes, 1990). Respondents utilize a 5-point Likert scale from 'strongly agree' to 'strongly disagree' with each of the 32 statements and then 4 scores are generated corresponding to pre-contemplation, contemplation, action and maintenance stages. It is an internally consistent scale, which can be adapted for different clinical problems. The URICA can be best employed to yield a single, continuous score of RTC as already demonstrated by the Project MATCH Research Group (1997).

The Readiness to Change Questionnaire is a 12-item scale developed to measure stage of change in non-treatment seeking alcohol drinkers (RCQ; Rollnick et al, 1992). Respondents rate each of the items on a Likert scale from 'strongly agree' to 'strongly disagree' and the highest score among pre-contemplation, contemplation and action scales is regarded as the current stage of change. This is a reliable instrument for use in medical settings and has been modified to produce a version to use in treatment (Heather et al, 1999).

The Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES; Miller & Tonigan, 1996) is 19-item instrument developed to measure RTC in substance users. Once again, respondents rate each item on a Likert scale from 'strongly agree' to 'strongly disagree' and are then assigned to one of three scales: recognition, taking steps and ambivalence.

The Cartoon Stage of Change Measure (C-SOC) is a non-verbal self-report instrument based on the TTM constructs developed by Wells et al (1998). The scale consists of a set of pictures of a gender and ethnicity- neutral character that participates in or abstains from illicit drug use. The participant is then invited to indicate how much the pictures are like or unlike them and their motivation is rated based on that choice. Because this measure involves limited language or

cognitive and abstract processing, it could potentially make a very suitable instrument for assessing RTC among patients with psychosis.

The Readiness Ruler (RR)

The Readiness Ruler (RR; Heather et al, 2008) is the revised version of the Readiness Ruler developed by LaBrie et al (2005) to assess readiness to change in excessive alcohol users. Heather et al (2008) rephrased the pre-contemplation item and deleted the maintenance stage from the initial Ruler to produce this single-item measure that allocates respondents to pre-contemplation (PC), contemplation (C), preparation (P) and action (A).

Using the Readiness to Change Questionnaire (RCQ- Rollnick et al, 1992) as the gold standard, the relationship between stages of change as allocated by the RCQ and patients' response on the Readiness Ruler was found to be highly significant ($\chi 2=37.5$, df=8, $p<0.0005$) in an examination of concurrent validity by Heather et al (2008). The contingency coefficient, measuring the degree of association between the two questionnaires, was 0.59 ($p<0.0005$). The correlation between the Readiness Ruler score and RCQ dimensional score was 0.47 (n=72, $p<0.0005$), which although highly significant, was lower than expected. When calculating the correlation for the two types of administration (self-report or interviewer-administered) separately, the significance remained (self-completion, rho=0.78, n=26, $p<0.0005$; interviewer-led, rho=0.72, n=26, $p<0.0005$). The difference between these two correlation coefficients was not significant (Z=0.45, p=0.34) (Heather et al, 2008).

This is a fairly new measure that still warrants further validation with regards to its power to measure change (Heather et al, 2008). As it was developed for excessive drinkers identified in primary care, this project will investigate its concurrent and predictive validity against the Readiness to Change Questionnaire- Treatment Version (RCQ-TV) for first-episode psychosis patients who use cannabis.

The Readiness To Change Questionnaire- Treatment Version (RCQ-TV)

The Readiness To Change Questionnaire – Treatment Version (RCQ-TV) (Heather et al, 1999) was originally designed to assess the motivational readiness to change drinking behaviour among excessive alcohol consumers. The questionnaire allocates participants to one of three stages outlined in the Trans-theoretical model developed by Prochaska and DiClemente (1983): pre-contemplation (PC), contemplation (C) and action (A). Participants complete the questionnaire about one substance only - usually the substance they use the most or are most concerned about. All items score from –2 (strongly disagree) through to +2 (strongly agree). Therefore, the maximum score for any stage can either be +8 or –8.

The stage with the highest positive score determines allocation. Tied scores are allocated to the stage furthest along the cycle of change from pre-contemplation.

For this study, the 15 self-report items have been modified to assess readiness to change cannabis use. It cannot be assumed that the instrument retains its psychometric properties with these modifications. Still, it was thought to be more valid to have a self-report measure than other stages of change scales that rely solely on clinician ratings. Also, it is assumed that although this would be the first presentation to services for psychotic symptoms, a number of patients would also be receiving concurrent treatment for substance use and the RCQ-TV would be more appropriate than the RCQ. It is the aim of this thesis to explore the concurrent and predictive validity of this questionnaire against the RR for first-episode psychosis patients who use cannabis.

It is evident that the above self-report measures of readiness to change were not developed with dual diagnosis patients in mind. In cases where they have been used for assessing motivation to change in patients with co-morbid mental health and substance use problems, evidence for their utility has been conflicting. Exploring to what extent motivation relates to changing cannabis use in patients with psychosis and developing appropriate instruments to measure their readiness to change would be a useful step.

1.6 Summary

Schizophrenia appears to be a multi-factorial disorder in which many susceptibility genes interact with various environmental risk factors including cannabis use. The experimental administration of Δ9-THC, the major psychoactive substance in cannabis, can produce a psychosis-like state in healthy individuals as well as exacerbate psychotic symptoms in patients with established schizophrenia. The rates of cannabis use are higher in patients with psychotic disorders than in the general population and longitudinal studies have consistently found that cannabis use in adolescence and early adult life is associated with later psychosis.

Despite years of research no consensus has been reached as to the reasons for increased rates of substance use in patients with psychosis. With the increased urgency to develop effective interventions for patients with psychosis who also use substances, investigating the motives that sustain cannabis use in this population is essential and it might facilitate the tailoring of successful interventions to individual needs. Motivating psychotic patients who use substances to commit to a process of behavioural change is difficult. Readiness to change substance use is likely to play an important part in the recovery process for psychotic patients who use substances and although the construct of RTC has been extensively investigated in primary substance users it is still uncertain whether it operates similarly in patients with co-morbid psychiatric disorders (Kolliakou et al, 2011).

1.7 Aims of the thesis

This thesis aims to investigate:

1. The association between cannabis use and mental health outcomes at 12 months.
2. The association between cannabis use and other substance use at baseline, 3 months and 12 months.
3. The self-reported reasons for cannabis use at baseline, 3 months and 12 months.

4. The association between readiness to change cannabis use at baseline and 3 months and cannabis use outcomes at 12 months.
5. The utility of the Readiness Ruler (RR) and the Readiness to Change Questionnaire- Treatment Version (RCQ-TV) in assessing motivation to change cannabis use.

1.8 Thesis outline

Chapter 2 will present the results from 3 systematic reviews: a) The effects of cannabis use on psychotic outcomes and its association with other drug use, b) the reasons for cannabis use in patients with psychosis and c) readiness to change as measure of cannabis use outcome in patients with psychosis.

Chapter 3 will discuss the general methodology of the PUMP study within which this thesis is nested.

Chapter 4 will describe the baseline socio-demographic and clinical characteristics of the sample. It will also present preliminary findings from baseline comparisons between participants and non- participants and cannabis users and non-users.

Chapter 5 will present and discuss results from the study on the effects of cannabis use on psychotic outcomes at 12 months as well as the association of cannabis and other drug use at baseline, 3 months and 12 months.

Chapter 6 will describe and discuss findings from the study on the reasons for cannabis use at baseline, 3 months and 12 months.

Chapter 7 will present and discuss results from the study on readiness to change, at baseline and 3 months, as a measure of cannabis use outcomes at 12 months.

Chapter 8 will comprise a summary of the findings from the experimental chapters and present general limitations of the PUMP study and biases in the thesis methods. Research and clinical implications of the findings will be discussed in this chapter as well.

Chapter 2 – Systematic reviews

2.1 Aims of the chapter

This chapter will describe the findings of 3 systematic reviews as follows:

1. The effects of cannabis use on psychotic outcomes and its association with other drug use in patients with psychosis.
2. The self-reported reasons for cannabis use in patients with psychosis.
3. Readiness to change cannabis use, as a predictor of cannabis use outcome, in patients with psychosis.

All reviews were completed between January and March 2010 to inform the development of the thesis.

2.2 Effects of cannabis use on psychotic outcomes and its association with other drug use

2.2.1 Methods

Criteria for selecting studies

Abstracts were considered eligible for full manuscript data extraction if they fulfilled the following criteria: (a) the design was prospective; (b) the study population included adolescents or adults (16-65 years old) with psychosis including schizophrenia or related psychotic disorders; (c) cannabis use was self-reported and/or verified by Urinary Drug Screen (UDS); (d) psychotic outcomes and other drug use were reported as primary or secondary outcomes; (e) abstracts and full papers were in English. Studies were excluded according to criteria in Figure 2.1.

Search Strategy

The following electronic libraries were searched: MEDLINE (1950 to 2009); PsycINFO (1806 to 2009) and EMBASE (1980 to 2009). The following search terms were used: 'psychosis' and 'cannabis'. The full search strategy is available in Table 2.1. The reference lists of included studies were searched for any

additional studies and corresponding authors and experts in the field were contacted for additional information on published and unpublished studies.

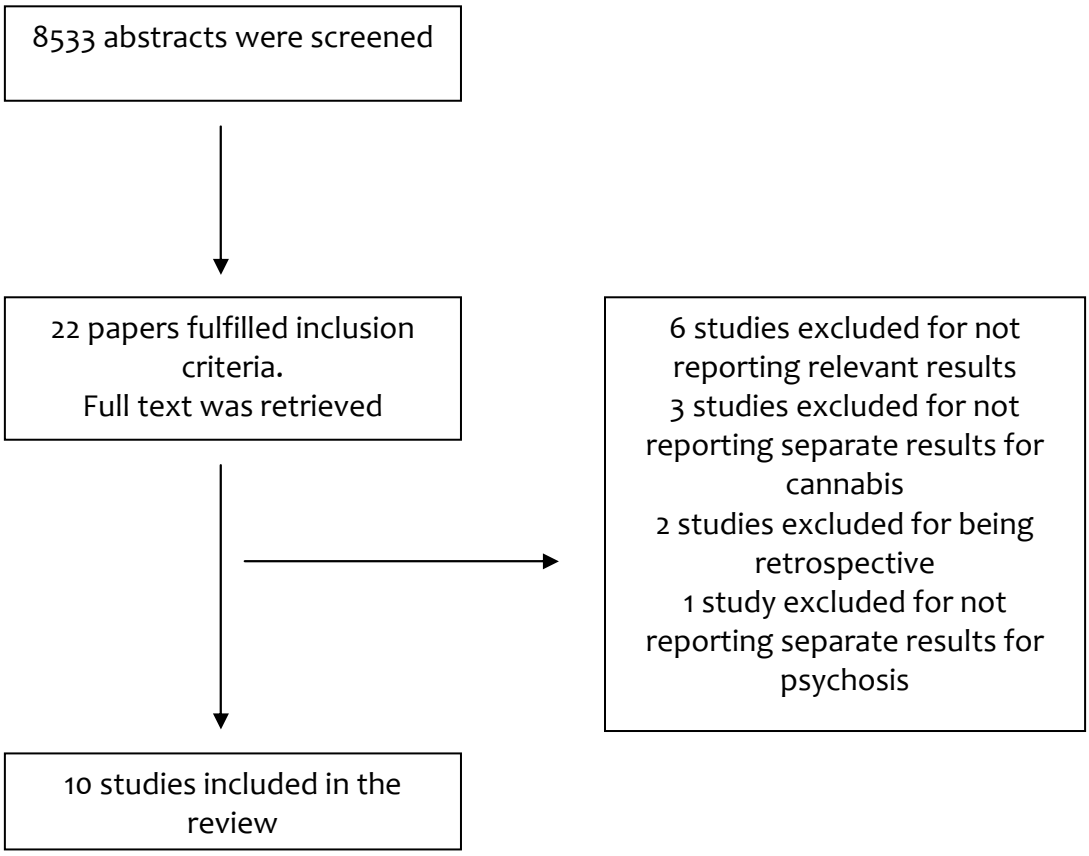
Table 2.1 Search strategy for systematic review of the effects of cannabis use on psychotic outcomes and other drug use in patients with psychosis.

	Search words
1	exp Cannabis/
2	cannabis.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
3	cannabis us*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
4	cannabis smok*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
5	drug us*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
6	patterns of drug us*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
7	patterns of substance us*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
8	patterns of cannabis us*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
9	6 or 3 or 7 or 2 or 8 or 1 or 4 or 5
10	exp Psychotic Disorders/
11	psychosis.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
12	psychot*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
13	11 or 10 or 12
14	9 and 13

Data extraction

Data were extracted from papers selected for further review. A standardised data extraction sheet was composed to record and code the following information (if available) from studies: author, country of origin and year; study methodology; sample characteristics (size, age, diagnosis); assessment of outcome (psychotic outcomes and other drug use)

Figure 2.1 Systematic review flow-chart of the effects of cannabis use on psychotic outcomes and its association with other drug use



2.2.2 *Results and discussion*

The search strategy yielded 8,533 abstracts from which 24 abstracts satisfied the criteria and full texts of the studies were retrieved. The 10 studies included in the systematic review are summarized in table 2.2

Table 2.2 Studies included in the systematic review of the effects of cannabis use on psychotic outcomes and other drug use in patients with psychosis.

Author Country Year	Study methodology	Sample characteristics (size, age, diagnosis)	Psychotic outcomes assessment			Drug use assessment
			Total symptoms	Positive Symptoms	Negative Symptoms	Other drug use
Addington and Addington Canada 2007	Prospective 3 year FU	142 patients, mean age= 25 years, DSM-IV	No	Yes	Yes	No
Degenhardt et al Australia 2007	Prospective 10-month FU	101 patients, 16-50 years old, diagnostic criteria not stated	Yes	No	No	No
Grech et al UK 2005	Prospective 4-year FU	98 patients, <60 years old, OPCRIT, DSM-III-R	No	Yes	Yes	No

Table 2.2 Studies included in the systematic review of the effects of cannabis use on psychotic outcomes and other drug use in patients with psychosis (cont.)

Author Country Year	Study methodology	Sample characteristics (size, age, diagnosis)	Psychotic outcomes assessment			Drug use assessment
			Total symptoms	Positive Symptoms	Negative Symptoms	Other drug use
Green et al USA 2004	Prospective 3-month FU	262 patients, 16-40 years old, DSM-IV	Yes	No	No	No
Hides et al Australia 2006	Prospective 6-month FU	81 patients, >16 years old, DSM-IV, OPCRIT	Yes	No	No	No
Hinton et al Australia 2007	Prospective 2-month FU (on average)	130 patients, 15-29 years old, DSM-IV	Yes	Yes	Yes	No

Table 2.2 Studies included in the systematic review of the effects of cannabis use on psychotic outcomes and other drug use in patients with psychosis (cont.)

Author Country Year	Study methodology	Sample characteristics (size, age, diagnosis)	Psychotic outcomes assessment			Drug use assessment
			Total symptoms	Positive Symptoms	Negative Symptoms	Other drug use
Linszen et al Netherlands 1994	Prospective 1 year FU	93 patients, 15-26 years old, DSM-III-R	Yes	No	Yes	No
Martinez-Aravalo et al Spain 1994	Prospective 1 year FU	62 patients, 18-30 years old, DSM-III	Yes	No	No	No
Stirling et al UK 2005	Prospective 10-12 year FU	69 patients, 16-50 years old, RDC and DSM-IV	No	Yes	Yes	No
Wade et al Australia 2006	Prospective 15-month FU	103 patients, 15-30 years old, DSM-IV	Yes	No	No	No

Psychotic outcomes

Total symptom severity

Martinez-Arevalo et al (1994) followed up 62 outpatients with a diagnosis of schizophrenia over one year and reported that 64% of patients who persistently smoked cannabis during the follow-up period and 37% of patients who smoked cannabis at baseline but subsequently stopped experienced a complete relapse in comparison to only 17% of non-smokers, even after adjusting for medication adherence and stresses. No adjustment for baseline confounders was undertaken as persistent use was assessed. Definition of relapse was not provided and cannabis exposure was not ascertained. No drug screening was utilised.

In a 12-month follow-up study of 93 outpatients with recent-onset schizophrenia or related disorders, Linszen et al (1994) found that cannabis abusers had significantly more and earlier psychotic relapses than non-abusers with heavy users experiencing more and even earlier relapses. The relationship remained significant after adjusting for baseline differences in age at admission, gender and alcohol use. Strict criteria were applied in rating cannabis exposure and grouping patients according to levels of use. Drug screening was not used to corroborate self-reports and patients with a primary alcohol or drug dependence or brief drug-related psychoses were excluded from participation.

In another follow-up (median 9 weeks and 4 days) study of 130 outpatients with first-episode psychosis, Hinton et al (2007) compared 4 groups of (i) those not using cannabis at either baseline and follow up; (ii) those who were using cannabis at both time points; (iii) those who were using at baseline but not at follow-up and (iv) those who were not using at baseline but were using at follow-up. They observed no significant differences between groups over time but found that those using cannabis at follow-up scored significantly higher than non-users on general psychopathology, social functioning and functional disability measures. No adjustment for confounders was carried out, as baseline comparisons between users and non-users did not reveal any differences. A time frame for cannabis use before admission to study was used to

rate exposure and all psychoses were included in the analysis. No drug screening was employed.

In a study of 101 outpatients with schizophrenia and related disorders, Degenhardt et al (2007) reported that cannabis use was associated with a small, albeit significant, increase in psychopathology that persisted after adjusting for age, gender, psychopathology, other drug use and month of data collection. A time frame for use before admission to study was used to define cannabis exposure, no drug screening was utilised and bipolar patients were excluded from participation.

Green et al (2004) found that there was no significant association between cannabis misuse and change in total PANSS scores from baseline to follow-up among 262 patients taking part in a 12-week RCT of haloperidol vs olanzapine for first-episode psychosis after adjusting for age of onset, duration of untreated psychosis and psychopathology. Current and lifetime cannabis users were merged to define the cannabis-using group, there were no drug screening procedures and patients with substance dependence were excluded from the study.

Positive and negative symptoms

In a prospective 15-month follow-up study of 103 in- and out-patients with first-episode psychosis, Wade et al (2006) found that patients who misused cannabis experienced higher rates of relapse of positive symptoms during follow-up compared to patients with alcohol misuse only and the association remained significant after controlling for the effects of gender, age, diagnosis, duration of untreated psychosis and medication compliance. There is no description of diagnoses included in the study, drug screening was not utilised and cannabis exposure was not established.

Hides et al (2006) followed up 81 inpatients with recent-onset psychosis over a period of 6 months and found that frequency of cannabis use (days per week) predicted psychotic relapse at 6 months and remained a significant predictor after adjusting for a number of demographic, functioning, substance

use, stress, family and clinical variables. Cannabis exposure and diagnostic groups were defined and drug screening was utilized to corroborate self-reported use.

Addington and Addington (2007), in a 3-year study of 142 in- and out-patients presenting with early psychosis, found that cannabis users had higher levels of positive symptoms at 1-, 2- and 3-year follow-up points than non-users. This remained significant after controlling for age at onset of use, age and gender. All psychoses were included in the analysis and definition of cannabis exposure was presented. No drug screening was utilised.

Grech et al (2005) followed up 98 inpatients with recent-onset psychosis over 4 years and found that there was an association between continued cannabis use and severity of positive symptoms at follow-up, which remained significant after adjusting for age at admission, ethnicity and gender. All psychoses were included and cannabis exposure was classified based on duration of use. No drug screening was applied.

Hinton et al (2007), as described previously, also found that cannabis users at follow-up reported more positive symptoms than non-users.

Stirling et al (2005), in a study of 69 inpatients with first-episode psychosis, reported no differences on positive symptoms between cannabis and non-cannabis users at 10-12 year follow-up. Adjustment for confounders was not undertaken as was definition of cannabis exposure not presented and urinary drug screen not utilised.

No association was observed in any of the studies between cannabis use and negative symptoms.

Other drug use

No studies looked at the association between cannabis and other drug use in patients with psychosis.

The effects of cannabis use on patients with an established psychotic disorder have been inconsistent. Three out of the four studies reported that persistent cannabis use was associated with increased relapse rates but one study failed to observe such a finding (Green et al, 2004). Similarly, five studies

showed that patients with ongoing cannabis use had more positive symptoms at follow-up than non-users but one did not report such significance (Stirling et al, 2005). No studies reported an effect of cannabis use on negative symptoms and no studies examined the relationship between cannabis and other drug use.

There are several methodological issues in the included studies. Sample sizes varied widely and analyses on smaller groups might have limited the power to detect associations otherwise significant and clinically important. Biomedical screening tests to corroborate substance use were only performed in one study (Hides et al, 2006). The increasing evidence that self-reported cannabis use from a range of populations including patients with psychosis is more accurate than collateral reports (Martin et al, 1988; Wolford et al, 1999; Selten et al, 2002) and the presence of high levels of substance use in the studies (i.e. Hinton et al, 2007) tend to challenge the notion that urine, blood or hair analysis would have been necessary but some authors argued that results would have been more convincing if they had used alternative confirmation of substance use (Linszen et al, 1994).

Studies that presented cross-sectional, rather than longitudinal, results were also included in the review (Linszen et al, 1994; Hinton et al, 2007; Addington and Addington, 2007). It would not have been possible for these studies to ascertain patterns of cannabis use in-between assessments so information on cannabis use might have lacked accuracy. Self-reported levels of cannabis use at follow-up don't necessarily reflect the actual pattern of use since baseline and it is possible that the true impact of cannabis use has been misreported. Definitions of cannabis exposure might partly explain this discrepancy since some studies defined cannabis use based on specific criteria (Hinton et al, 2007) whereas others did not (Wade et al, 2006). Similarly, some studies grouped users based on frequency or quantity of cannabis use (Addington and Addington, 2007). Studies also varied in their definitions of psychotic diagnosis with a couple of studies excluding substance-induced psychosis or bipolar disorder. Early/recent/first-episode psychosis appeared to be used interchangeably although these terms indicated the presence of functional psychosis with varying durations. Adjustment for confounders was also not

systematically carried out. Finally, although the sample sizes reported above represent the number of patients whose data were available at all assessment points, Zammit et al (2008) point out that the high loss to follow-up and lack of statistical power (estimated sufficient sample size of 250) might have led to the underestimation of the strength of any of the associations of interest.

2.3 Current reasons for cannabis use in patients with psychosis

2.3.1 Methods

Criteria for selecting studies

Abstracts were considered eligible for full manuscript data extraction if they fulfilled the following criteria: (a) the design was observational and prospective; (b) the study population included adolescents or adults (16-65 years old) with psychosis including schizophrenia or related psychotic disorders; (c) cannabis use was self-reported and/or verified by Urinary Drug Screen (UDS); (d) current reasons for cannabis use as a primary or secondary outcome were included; and (e) abstracts and full papers were in English. Studies were excluded according to criteria in Figure 2.2.

Search Strategy

The following electronic libraries were searched: MEDLINE (1950 to 2009); PsycINFO (1806 to 2009) and EMBASE (1980 to 2009). The following search terms were used: 'psychosis' and 'reasons for cannabis, substance and drug use'. The full search strategy is available in Table 2.3. The reference lists of included studies were searched for any additional studies and corresponding authors and experts in the field were contacted for additional information on published and unpublished studies.

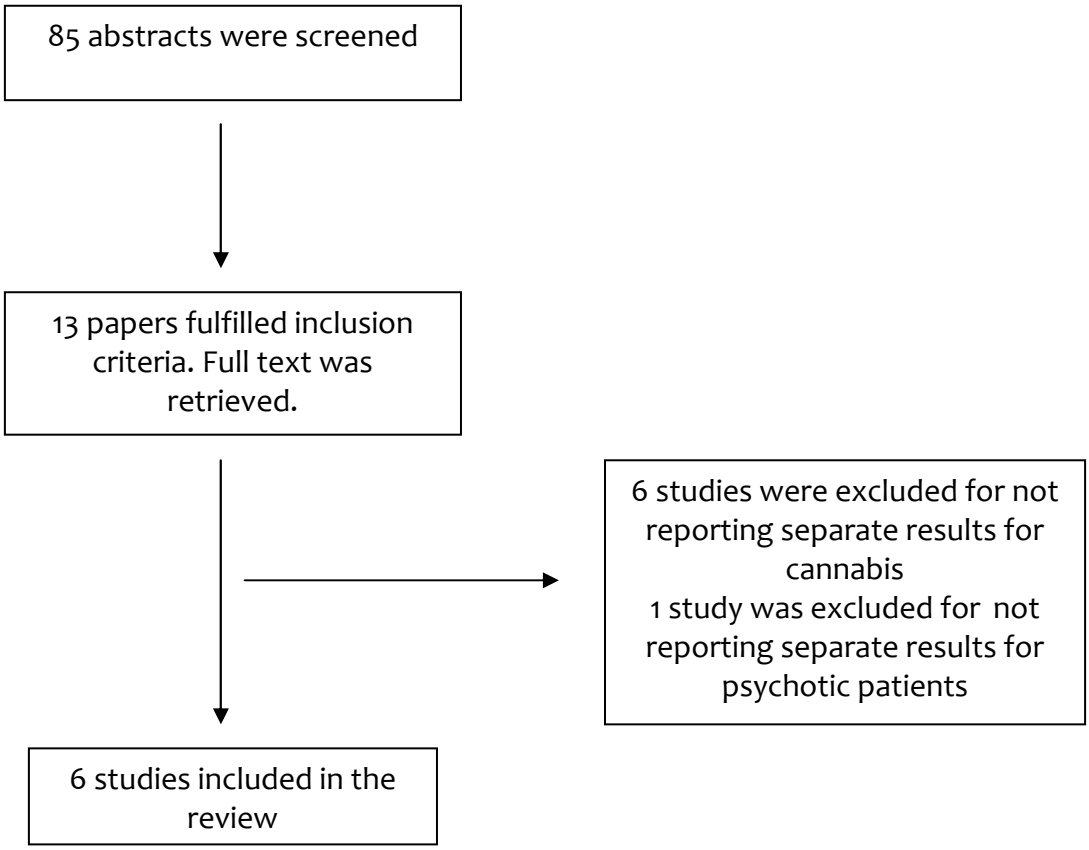
Table 2.3 Search strategy for systematic review of the current reasons for cannabis use in patients with psychosis.

	Search words
1	exp Psychotic Disorders/
2	psychosis.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
3	psychot*.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
4	or/1-3
5	reasons for cannabis us*.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
6	reasons for drug us*.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
7	reasons for substance us*.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
8	or/ 5-7
9	4 and 8

Data extraction

Data were extracted from papers selected for further review. A standardized data extraction sheet was composed to record and code the following information (if available) from studies: author, country of origin and year; assessment measures; sample characteristics (size, diagnosis); assessment of outcome (reasons for use).

Figure 2.2 Systematic review flow-chart of current reasons for cannabis use



2.3.2 Results and discussion

The search strategy yielded 85 abstracts from which 13 abstracts satisfied the criteria and full texts of the studies were retrieved. Six studies were excluded for not reporting separate results for cannabis and one study was excluded for not reporting separate results for psychotic patients. The six studies included in the systematic review are summarized in Table 2.4. The reasons were categorized according to Spencer et al's (Spencer et al, 2002) modification of the Drinking Motives Questionnaire (Cooper, 1994) to include reasons specifically related to psychiatric symptoms: 'enhancement/ intoxication', 'social effects, conformity/ acceptance', 'coping with positive symptoms', 'coping with dysphoria and negative symptoms' and 'coping with medication side effects'.

Table 2.4 Studies included in the systematic review of the current reasons for cannabis use in patients with psychosis.

Author Country Year	Assessment measure	Sample characteristics (size, diagnosis)	REASONS FOR CANNABIS USE				
			Enhancement, intoxication	**Social effects, conformity/ acceptance**	**Coping with positive symptoms**	**Coping with dysphoria and negative symptoms**	**Coping with medication side effects**
Addington and Duchak Canada 1997	Questionnaire (Dixon et al, 1990)	21 cannabis users with schizophrenia (DSM-III-R)	95%- pleasure 95%- get high 48%- talkative 48%- feel more emotions 62%- more interests 57%- more thoughts 33%- concentrate better 29%- energy levels 24%- sexual interest 5%- increase 'voices'	71%- go along with the group	40%- voices 19%- suspiciousness	81%- to relax 81%- relieve depression 24%- decrease tiredness	Not reported

Table 2.4 Studies included in the systematic review of the current reasons for cannabis use in patients with psychosis (cont.)

Author Country Year	Assessment measures	Sample characteristics (size, diagnosis)	REASONS FOR CANNABIS USE				
			Enhancement, intoxication	**Social effects, conformity/ acceptance**	**Coping with positive symptoms**	**Coping with dysphoria and negative symptoms**	**Coping with medication side effects**
Fowler et al Australia 1998	Interview	58 cannabis users with schizophrenia (DSM-III-R)	41%- intoxication effects	58%- social reasons	Not reported	62%- relieve dysphoria	18.5%- to make side effects more tolerable

Table 2.4 Studies included in the systematic review of the current reasons for cannabis use in patients with psychosis (cont.)

Author Country Year	Assessment measures	Sample characteristics (size, diagnosis)	REASONS FOR CANNABIS USE				
			Enhancement, intoxication	**Social effects, conformity/ acceptance**	**Coping with positive symptoms**	**Coping with dysphoria and negative symptoms**	**Coping with medication side effects**
Goswami et al India 2004	Questionnaire based on Dixon et al, 1991.	5 cannabis users with schizophrenia (DSM-IV)	80%- get high 100%- to increase pleasure 40%- to increase energy 40%- to increase emotions 40%- to talk more 40%- to be more creative 40%- to increase concentration 40%- to work and study better 40%- to increase confidence	40%- to go along with the group 20%- to increase socialization	40%- to decrease hallucinations 40%- to decrease suspiciousness	80%- to relax 60%- to decrease anxiety 40%- to increase sleep 40%- decrease depression 20%- to increase appetite	8%- to decrease side effects of medication

Table 2.4 Studies included in the systematic review of the current reasons for cannabis use in patients with psychosis (cont.)

Author Country Year	Assessment measures	Sample characteristics (size, diagnosis)	REASONS FOR CANNABIS USE				
			Enhancement, intoxication	**Social effects, conformity/ acceptance**	**Coping with positive symptoms**	**Coping with dysphoria and negative symptoms**	**Coping with medication side effects**
Green et al Australia 2004	Interview	45 male cannabis users with psychosis (DSM-IV)	4%- cognitive enhancement 36%- mood alteration 11%- physical enhancement 16%- entertainment 20%- wanted to 11%- habit	38%- social activity/ offered	Not reported	27%- anxiety depression 22%- boredom 7%- other negative mood 2%- relaxation	Not in top 10 reasons

Table 2.4 Studies included in the systematic review of the current reasons for cannabis use in patients with psychosis (cont.)

Author Country Year	Assessment measures	Sample characteristics (size, diagnosis)	REASONS FOR CANNABIS USE				
			Enhancement, intoxication	**Social effects, conformity/ acceptance**	**Coping with positive symptoms**	**Coping with dysphoria and negative symptoms**	**Coping with medication side effects**
Schaub et al Switzerland 2008	Questionnaire developed for the study	36 cannabis users with schizophrenia (criteria not stated)	83.3%- get high 72.2%- pleasure - talkative 58.3%- increase emotions and feelings 55.6%- more creative 33.3%- arrange thoughts 33.3%- work better 30.6%- increase energy 30.6% concentrate better	33.3%- go along with the group 27.8%- talk better to others	19.3%- decrease hallucinations	88.9%- to relax 69.4%- to sleep better 63.9%- reduce boredom 41.7%-reduce feelings of depression	Not reported

Table 2.4 Studies included in the systematic review of the current reasons for cannabis use in patients with psychosis (cont.)

Author Country Year	Assessment measures	Sample characteristics (size, diagnosis)	REASONS FOR CANNABIS USE				
			Enhancement, intoxication	**Social effects, conformity/ acceptance**	**Coping with positive symptoms**	**Coping with dysphoria and negative symptoms**	**Coping with medication side effects**
Schofield et al. Australia 2006	Questionnaire (Dixon et al., 1991)	49 cannabis users with schizophrenia (criteria not stated)	39%- feel good about oneself	81%- something to do with friends	11%- decrease voices 8%- reduce paranoia	86%- to relax 79%- relieve boredom 58%- improve sleep 49%- reduce anxiety	Not reported

Addington and Duchak (1997) investigated reasons for cannabis use among patients with a diagnosis of schizophrenia. The most frequent reasons were to increase pleasure and to get high, to relax and reduce depression and to be more sociable. In 2004, Green and colleagues compared male cannabis users with psychosis to a cannabis-using control group without psychosis. Patients with psychosis most commonly reported using cannabis for positive mood alteration, coping with negative affect and for social activity reasons. Relaxation was the least popular reason for cannabis use together with general coping with negative mood and cognitive enhancement. Availability of cannabis seemed to be a very important reason for its use. Schofield et al (2006) had the benefit of a larger sample diagnosed with a schizophrenia spectrum disorder. Patients again reported using cannabis to relax, to have as an activity with friends and to relieve boredom. Less than a quarter of patients used cannabis to reduce the side effects of antipsychotic medication, or to reduce positive symptoms. Fowler et al (1998) explored reasons for cannabis use amongst the largest sample of patients i.e. 58. Using cannabis to reduce dysphoria was the most common reason, succeeded by social reasons and intoxication effects. However, they argued that their sample was unrepresentative as the patients were from outpatient clinics only and there were more males than females. In Switzerland, Schaub et al (2008) used a case-control design and investigated reasons for cannabis use among outpatients with schizophrenia and matched controls. Using a questionnaire, they found that the majority of patients used cannabis to relax, get high and increase pleasure. The only significantly different reason between the two groups was that more patients than controls reported taking cannabis to relieve boredom. Goswami et al (2004) were only able to examine reasons for cannabis use in 5 dually diagnosed patients. All 5 patients stated they used cannabis to increase pleasure and 4 out of the 5 patients stated they used cannabis to get high, relax and satisfy curiosity.

Methodological problems are quite evident in the above studies. Not all employed standardized criteria for diagnosis (Schofield et al, 2006; Schaub et al, 2008) and sample sizes varied, with a tendency towards smaller groups (Goswami et al, 2004). Some studies focused on co-morbid groups where

patients had an established, and possibly primary, substance use disorder (Addington and Duchak, 1997; Fowler et al, 1998) while others included patients who were just cannabis users (Schofield et al, 2006; Green et al, 2004; Schaub et al, 2008). In addition, a variety of techniques and instruments were used to assess reasons for use. Both interviews and questionnaires were utilized, and reasons were identified through free response, open-ended questions or fixed lists.

Dekker et al (2009) point out that older studies may have taken place when concentrations of THC in cannabis were lower than they are nowadays, which may have affected patients' experiences of the drug. Schaub et al (2008) argue that most studies did not investigate the medications patients were taking, and therefore some patients may have been taking cannabis to reduce the side effects of older typical antipsychotics.

Despite these inconsistencies, it does appear that patients with psychosis use cannabis for the same reasons as the general population (Green et al, 2004). Patients smoke cannabis mostly because of its 'enhancing' effects, and 'to get high' or to reduce negative states such as depression and dysphoria. Social reasons follow closely, with 'relief from voices and other positive symptoms' being less important. 'Coping with medication side effects' was the least popular motive, and thus there was little support for the self-medication hypothesis. Although this hypothesis cannot be altogether dismissed due to the aforementioned methodological flaws in the studies, the results point more towards an alleviation of dysphoria.

Further research in this area requires adequate sample size and structured criteria for diagnosis of psychiatric illness and substance use. There should be emphasis on the use of validated instruments for assessing reasons for cannabis use, rather than individualistic interviews that are difficult to replicate or apply to future studies. Urine drug screens should be used to compliment self-reported use. It would also be useful to investigate the relationship between reasons for use and symptomatology and explore this over a follow-up period. This would shed light on whether cannabis use does actually alleviate dysphoric experiences and reduce social withdrawal and boredom.

2.4 Readiness to change as a predictor of cannabis use outcome

2.4.1 Methods

Criteria for selecting studies

Abstracts were considered eligible for full manuscript data extraction if they fulfilled the following criteria: (a) The design was observational and prospective; (b) The study population included adolescents or adults (16-65 years old) with psychosis including schizophrenia or related psychotic disorders; (c) Cannabis use was either self-reported and/or verified by positive urinalysis or hair analysis; (d) Measurement of readiness to change as a primary or secondary outcome was included; (e) Abstracts and full papers were in English. Studies were excluded according to criteria in Figure 2.3.

Search strategy

The following electronic libraries were searched: MEDLINE (1950 to 2009); PsycINFO (1806 to 2009) and EMBASE (1980 to 2009). The following search terms were used: 'psychosis' and 'readiness/motivation to change'. The full search strategy is available in Table 2.5. The reference lists of included studies were searched for any additional studies and corresponding authors and experts in the field were contacted for additional information on published and unpublished studies.

Table 2.5 Search strategy for systematic review of readiness to change cannabis use, as a predictor of outcome, in patients with psychosis.

	Search words
1	exp Psychotic Disorders/
2	psychosis.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
3	psychot*.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
4	or/1-4
5	Readiness to change.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
6	Motivation to change.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
7	Motivation to quit.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
8	Behaviour* change mp. [mp=title, original title, abstract, name of substance word, subject heading word]
9	Or/5-8
10	4 and 9

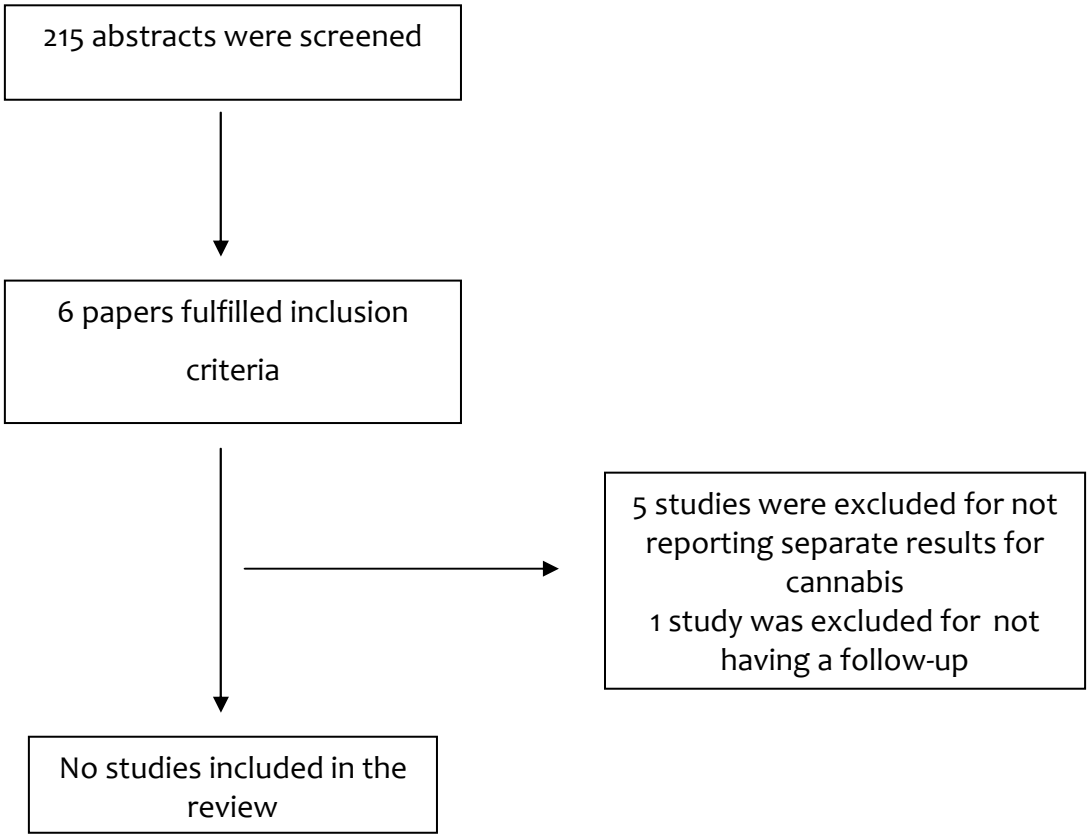
Data extraction

Data were extracted from papers selected for further review. A standardized data extraction sheet was composed to record and code the following information (if available) from studies: author, country of origin and year; assessment of readiness to change; sample characteristics (size, age, diagnosis); assessment and classification of outcome (reduction or cessation of cannabis use); follow-up period.

2.4.2 Results and discussion

The search strategy yielded 215 abstracts, from which 6 abstracts satisfied the criteria and full text of the study was retrieved. Of these six studies, five did not report separate results for cannabis use and one did not have a follow-up period. No studies were eligible for inclusion.

Figure 2.3 Systematic review flowchart of readiness to change, as a predictor of outcome, in patients with psychosis.



2.5 Strengths and limitations of systematic reviews

One of the main strengths of these reviews is that they are based on principles derived from the Cochrane Collaboration methods, such as an a priori protocol. Experts in the field were contacted for further papers to ensure results were as comprehensive as possible. The same quality can be attributed to the search strategies, which were very extensive and detailed and included psychosis rather than schizophrenia as it was judged to be broader. Lastly, it was decided

not to limit the searches to cannabis but include substance use in general to ensure they were as inclusive as possible in obtaining relevant papers.

A possible limitation of the reviews is the exclusion of studies that reported substance use in general and the inclusion of only those focused on cannabis use. Two reasons led to this decision. Firstly, use of individual substances may have different prognostic effects in patients with psychosis, be sustained for different reasons and motivate behaviour change to varying degrees. Although cannabis is one of the most popular substances among psychotic patients and research has been extensively carried out to look at the effects of persistent use in this population, results have not always been conclusive. Similarly, research has not been extensively carried out on the reasons for such high rates of use in this population and the limited results have been largely uncertain. Including general drug use in our review would not have yielded sufficient detail on why patients use cannabis in particular.

Also retrospective studies were excluded to minimise recall bias. Although establishing cause and effect in studies with so many possible confounders (i.e. baseline symptom severity and functioning, other drug use) is an already difficult task, including prospective studies only provided a more accurate account of patterns of cannabis use, readiness to change and effect on prognosis and actual behaviour change.

Finally, the search was limited to studies of patients diagnosed with psychosis and related disorders only. It was important to consider psychosis as an independent risk factor for cannabis use, which would not have been as accurately investigated if we had included other psychiatric illnesses.

2.6 Summary

The systematic reviews performed on the effects of cannabis use on psychotic outcomes and reasons for cannabis use have generated conflicting findings. Literature so far has shown negative effects of cannabis use on psychotic prognosis but some research has not observed such results. Mood enhancing and social reasons for cannabis use have been largely endorsed but a small number of patients still reported using cannabis motivated by self-

medication. We were unable to find relevant literature reporting on the association between cannabis use and other drug use or readiness to change and cannabis use outcomes. In the next chapter, the general methodology of the wider study, within which this thesis is nested, will be described.

Chapter 3 – General methodology

3.1 Aims of the chapter

The data presented within this thesis are nested within the Physical health and substance Use Measures in first-onset Psychosis (PUMP) study and thus general methodological procedures for this project are identical to the main study. This chapter will:

1. Outline the aims and hypotheses of the PUMP study.
2. Provide an overview of the PUMP study (design, setting, sample selection and recruitment procedure) and summarize the study data collection schedule.

3.2 The PUMP study

3.2.1 Main aims and hypotheses of the PUMP study

1. Patients with their first episode of psychosis who have unhealthy lifestyle habits are more likely to develop the features of the metabolic syndrome (central obesity plus one of the following: raised triglycerides, reduced HDL cholesterol, raised blood pressure, raised fasting plasma glucose) (Alberti et al, 2006) over a one-year follow-up period than those with healthier lifestyles allowing for relevant confounding factors such as age, ethnicity and family history of metabolic diseases.
2. Patients with their first episode of psychosis who use cannabis and other substances will have more psychotic symptoms at 12-month follow-up compared to non-substance users.
3. The rate of progression of metabolic (glucose and lipids) dysregulation over a 12-month period will be greater in those taking clozapine and olanzapine compared to other antipsychotics.

3.2.2 The PUMP study methodology

Design

The PUMP study is a prospective observational cohort of patients, with a first episode of psychosis, who were followed up for a minimum of 12 months to

test the association between lifestyle (diet, exercise, and substance use) and antipsychotic medication factors with a) psychotic symptoms and b) components of the metabolic syndrome.

Setting

Patients were recruited from the boroughs of the South London and Maudsley (SLaM) NHS Trust: Southwark, Lambeth, Croydon and Lewisham. Participants were also recruited from the Bromley and Greenwich boroughs under the Oxleas NHS Trust, as well as from West Sussex and Brighton under the Sussex NHS Trust. Both inpatient and outpatient services were targeted. Ethics approval was granted by the Ethics Committee at the Institute of Psychiatry (REC Ref No. 08/H0807/53). The PUMP study was funded by the National Institute for Health Research (NIHR) Programme Grants for Applied Research in the Department of Health [RP-PG-0606-1049].

Sample selection

Patients presenting with a first-episode psychosis were consecutively approached for participation in the study if they were:

1. aged 16-65 years.
2. presenting to services within the last 6 months with a first-onset psychotic disorder (ICD 10 definition of functional psychosis).
3. experiencing positive psychotic symptoms of at least 7 days duration.

Patients were excluded from the study if they met any of the following criteria:

1. evidence of psychotic symptoms precipitated by an organic cause.
2. moderate or severe learning disabilities.
3. major medical or neurological illness.
4. insufficient command of English to complete assessments.
5. contact with health services (GP or psychiatric) for psychosis longer than 6 months from identification.
6. pregnancy.

Recruitment procedure

Baseline

Baseline data for the PUMP study were gathered between May 2008 and July 2011.

Inpatients

Researchers screened for potential participants at the beginning of each week through a variety of means to ensure the maximum level of recruitment and minimise selection bias. They took a list of all new admissions to SLaM and Oxleas wards (including intra-hospital transfers), which may treat psychotic patients, and screened clinical notes to assess for eligibility. This was supplemented with regular communication with doctors, nurses and healthcare assistants on the wards.

Outpatients

In the Sussex NHS Trust recruitment was carried out solely from community and home treatment teams. This method also complemented ward recruitment in SLaM and Oxleas where resources were available to cover these. Researchers attended weekly team meetings where the caselog was discussed. New referrals were identified and screening followed an identical procedure to that of the inpatients above. There were a number of teams that did not produce a caselog to screen. In this case, care coordinators and teams leaders were approached and invited to suggest patients they thought might be suitable for the study. It is therefore possible that in these teams some eligible patients may have not been identified.

When a patient was deemed suitable and after checking with the ward or community team that it was safe to proceed, patients would be approached and invited to participate in the study. The specifics of the project would be fully described and patients would be given the information and consent sheets. If patients were willing to participate and able to give informed consent, they were requested to read through the information sheet, invited to ask any questions and confirm that they fully understood the study. Afterwards, they would be reassured that they could withdraw from the study at any time without having to give a reason and asked to sign the consent form. On occasions, patients would

ask researchers to visit them in the future to discuss participation or leave the information for them to consider at a separate time. Consequently, some patients would have been approached on several occasions as requested. If patients asked not to be approached again, this of course was respected.

3- and 12-month follow-ups

Three-month follow-ups were completed by December 2010 and 12-month follow-ups by July 2012.

At 3 and 12 months post-consent, researchers re-contacted all patients who had consented to the study regardless of completion status at baseline and invited them to take part in the follow-ups. Patients who were excluded or had withdrawn from the study post-consent were not re-contacted.

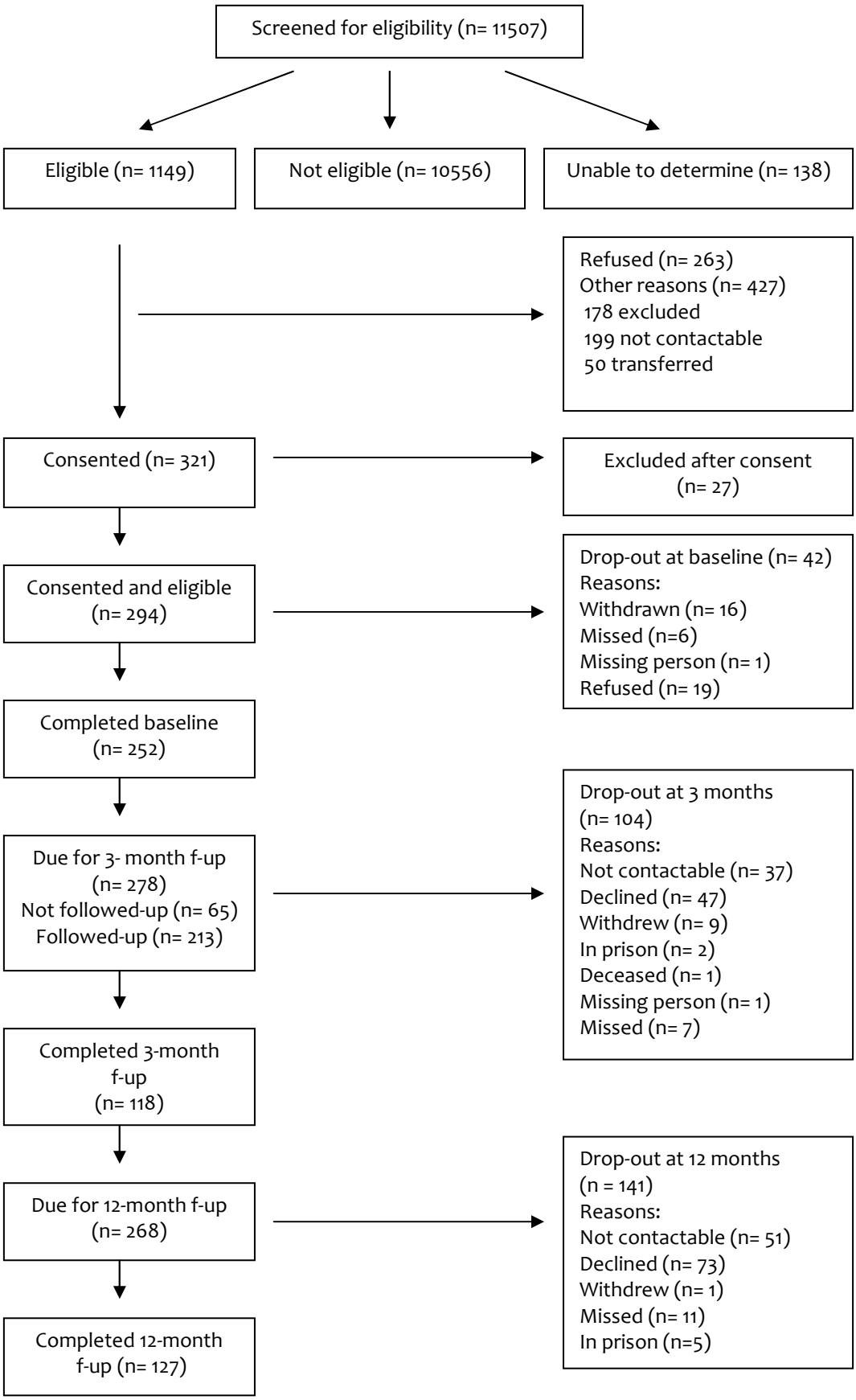
Once again a variety of procedures was employed to maximise retention rates and follow-up completion. The patients' clinical notes were checked to establish whether they were in hospital or in the community. If the patient was still in hospital, the ward team would be contacted and an appointment to visit would be arranged. The follow-up process would be explained and the patient would be invited to complete the assessments.

If the patient had been discharged, researchers would utilize the contact details (phone, email, address, nominated friend/relative) provided by the patient at consent to get in touch. Firstly, all patients were sent a letter 3 months before due follow-up date to remind them of the study and ask them to return a pre-paid reply slip to indicate whether they would be interested in participating and provide their preferred method of contact. If a patient replied they did not wish to complete follow-up assessments, this would be honoured and no further contact would be pursued. In cases where no reply was received and other means proved ineffective, the following professionals (if permission had been granted by patient at consent) would be contacted to help establish contact: (i) care coordinator and/or (ii) other assigned health-care worker. It was quite often the case that clinical notes were not informative enough to help researchers identify whether patients were still in contact with services. In this instance, and only if consent had been given by patient at baseline, researchers would contact the last known GP the patient was registered with. If the GP was not able to

provide researchers with up-to-date contact details, the patient would be classified as non-contactable and no attempt for further contact would ensue. In the case where the patient had not provided consent to contact their assigned health-care professional or GP, no further action would be taken and the patient would be classified as non-contactable.

A summary of the recruitment and completion rates of the PUMP study at the 3 time-points is provided in Figure 3.1.

Figure 3.1 PUMP study recruitment and completion rates



Measures

The full data collection schedule took 4 hours to complete and comprised a number of assessments collected at baseline, 3 months and 12 months. Table 3.1 summarizes the thesis hypotheses, assessment instruments and plan for analysis.

Table 3.1 Thesis hypotheses, assessment instruments and analysis plan

Hypotheses	Instruments	Analysis plan
CHAPTER 5		
1. Patients who use cannabis at 12 months will have higher total symptom severity than those who are not current users or have never used cannabis. 2. Patients who use cannabis at 12 months will have more positive symptoms than those who are not current users or have never used cannabis. 3. At each time point, patients who use cannabis will be more likely to use other drugs than those who are not current users or have never used cannabis.	• Positive and Negative Syndrome Scale (PANSS) • Cannabis Experience Questionnaire (CEQ)	• Hypotheses 1 and 2 a) Chi-square tests, independent sample t-tests and Mann-Whitney tests b) Univariate and multivariate linear regressions • Hypothesis 3: a) Chi-square tests, independent sample t-tests, Mann Whitney tests and Fisher's exact tests b) Univariate and multivariate logistic regressions

Table 3.1 Thesis hypotheses, assessment instruments and analysis plan (cont.)

Hypotheses	Instruments	Analysis plan
CHAPTER 6		
1. At each time point, patients who use cannabis will be more likely to do so because of its enhancing effects and for social reasons rather than to 'self-medicate'. 2. The changes in reasons for cannabis use across the 3 time points will be examined in a post-hoc analysis.	• Reasons for Use Scale (RFUS)	• Hypothesis 1 a) Paired-sample t-tests • Hypothesis 2 b) Random intercept model
CHAPTER 7		
1. Readiness to change at baseline according to the Readiness Ruler will be associated with cannabis non-use at 12 months. 2. Readiness to change at 3 months according to the Readiness Ruler rather than the Readiness to Change Questionnaire-Treatment Version will be associated with cannabis non-use at 12 months.	• Readiness Ruler (RR) • Readiness To Change Questionnaire- Treatment Version (RCQ-TV)	• Hypotheses 1 and 2 a) Chi-square tests, independent sample t-tests, Mann Whitney tests and Fisher's exact tests b) Univariate and multivariate logistic regressions

3.3 Thesis rationale

Numerous studies have shown that patients with psychosis are more likely to use illicit drugs than the general population with cannabis being the most popular. There is evidence that cannabis use can contribute to the onset of schizophrenia and poor outcome in patients with established psychosis. Therefore, understanding why patients use cannabis and whether they are motivated to change their habits is important. To date, there has been little support for the 'self-medication' hypothesis, while the literature points more towards an 'alleviation of dysphoria' model. There is a lack of research as to whether psychotic patients are ready to change their use of cannabis, which has implications for identifying which treatment strategies are likely to be effective. The purpose of this thesis is to examine the reasons for cannabis use in first-episode psychosis as well as report a preliminary investigation of motivational processes in cannabis-using behaviour in patients with psychosis and its effects on cannabis use outcomes. The thesis design, measures and analysis plan are presented in table 3.2.

In the next chapter, the baseline characteristics as well as comparisons between participants and non-participants and cannabis users and non-users by socio-demographic and clinical variables will be examined.

3.4 Candidate's contribution

This thesis was an extension of one of the main PUMP hypothesis, namely that patients who use cannabis and other substances will have more psychotic symptoms at 12 months than non-users. Anna developed this into a full PhD proposal by proposing two further research ideas to investigate reasons for cannabis use and readiness to change in first-episode psychosis. Anna was solely responsible for identifying the appropriate instruments to examine reasons for use and readiness to change, training researchers in their application and developing the hypotheses to test the research questions.

Anna was one of the first researchers to join the PUMP team in 2008 and continued as a Research Worker and PhD student until the end of the study in July 2012. Anna's main responsibilities comprised the identification of potentially eligible participants, recruitment and assessment of these at baseline, 3 months and 12 months in SLaM as well as Oxleas and providing supervision and training to new researchers. Anna was also responsible for blood and saliva collections from consented participants. Data were entered by the Abacus company and Anna was solely responsible for all aspects of data management i.e. liaising with the company, cleaning and maintaining the PUMP data set and preparing it for analysis.

Anna conducted all of the analysis presented in this thesis following supervision from Professor Khalida Ismail, Dr Zerrin Atakan, Dr Daniel Stahl (senior statistician) and Ms Hannah Sallis (junior statistician). Anna wrote this thesis in its entirety under the supervision of Professor Khalida Ismail and Dr Zerrin Atakan.

3.5 Limitations of the PUMP study and methodological decisions for thesis

The PUMP study collaborated with the Genetics and Psychosis study (GAP) for the duration of the 4-year project. This offered the advantage of a large number of researchers working in recruitment and assessment for both studies but unfortunately meant that the joint data collection schedules took almost 12 hours to complete at baseline and 8 hours at 3- and 12-month follow-ups.

Considering the burden on potential participants and after careful supervision, Anna was able to include the RFU scale and the RR at baseline but

the RTCQ-TV was only used at 3 months as it was considered lengthy by the team. Thus, the utility of the RR and the RCQ-TV in assessing changes in cannabis use at the 12-month follow-up was only tested at 3 months. Due to the length of the assessments and the fact that both studies' protocols had already been approved, it was also not possible to replace the CEQ with an instrument more suitable to record patterns of cannabis use or complement this questionnaire with a severity of dependence scale and/or a diagnostic instrument for cannabis use disorder. One item from the CEQ was used to categorise participants into current cannabis users or non-users at each time point.

Although the PUMP study continued collecting data until July 2012, the thesis had to be completed before the end of the study according to the PhD submission timetable. Analysis based on diagnosis was not possible as data, which might have been available later on, were incomplete at the time of submission. Similarly, 12-month follow assessments continued for the PUMP study so Anna was not able to make full use of data collected for the duration of the study.

Due to the limitations with regards to available data at the time of thesis preparation and submission as well as the high drop-out rate, it was not appropriate to validly perform a repeated-measures analysis as it was initially planned. The sample size was not large enough to allow for changes in cannabis use and psychopathology to be repeatedly examined at the 3 time points in a prospective manner. Instead, to test the effects of cannabis use on psychopathology, in chapter 5, a series of univariate and multivariate regressions were performed at 12 months while controlling for confounders as identified from differences between cannabis users and non-users at baseline. At 12-month follow-up issues arose with missing psychopathology data from the PANSS subscales. Percentages of these missing data and the reasons for not inputting them will be discussed in Chapter 5.

Chapter 4 – Basic characteristics and preliminary analysis

4.1 Synopsis

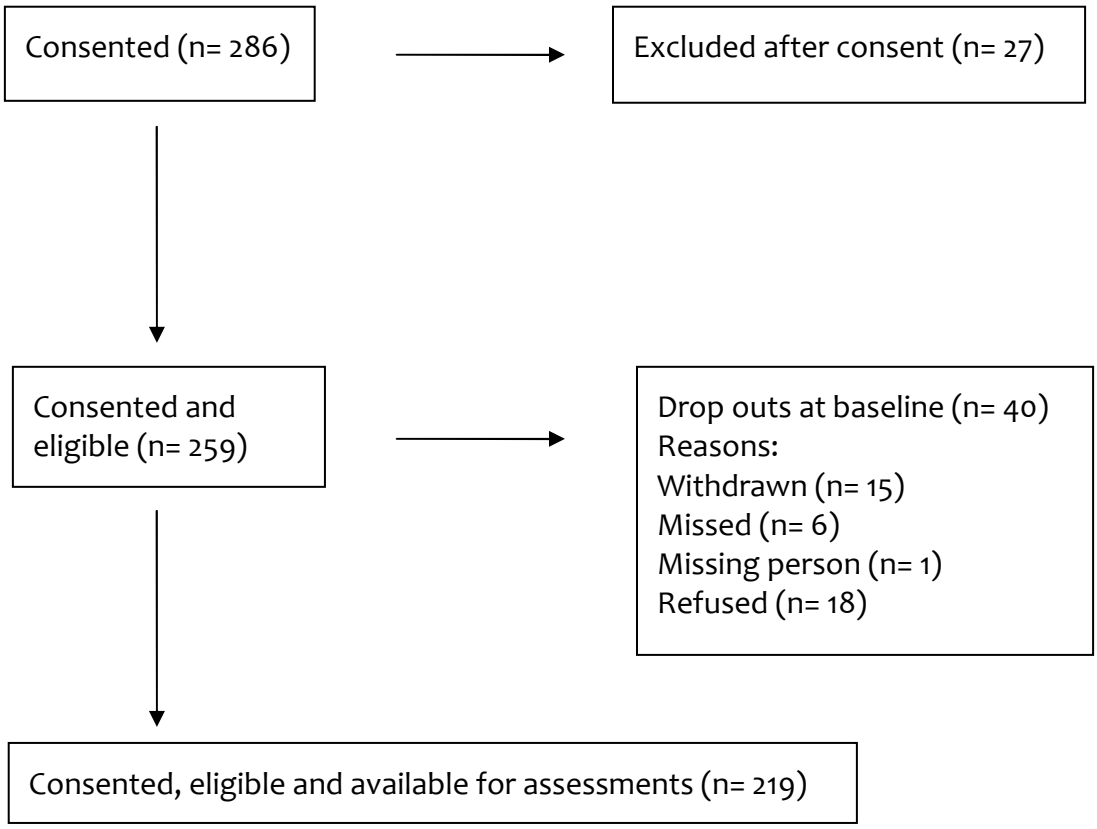
This chapter examines the baseline characteristics of the sample. The measures used to collect these data will be briefly described. Socio-demographic characteristics of the sample will be presented together with information on diagnosis, lifetime and current tobacco, alcohol, cannabis and other drug use. Data on psychopathology and stressful events as well as medication compliance will be reported. Differences between participants and non-participants (drop-outs) based on age, gender and ethnicity will be examined. Lastly, current cannabis users and non-users will be compared based on the aforementioned measures. These comparisons are important for identifying potential systematic biases and confounders that will need to be controlled for in later analyses.

4.2 Sample selection

A final sample of 321 patients was recruited in the PUMP study between May 2008 and July 2011. A sample of 286 patients recruited and followed up between May 2008 and December 2011 was included in this thesis. Of the 286 patients, 27 were subsequently excluded for not satisfying the criteria for a first episode of psychosis or needing a translator and a further 40 patients dropped out at baseline leaving a final sample of 219 patients available for assessments. A summary of baseline recruitment and retention rates is shown in Figure 4.1.

Due to the long battery of assessments included in the PUMP study and the relatively unstable nature of a first-episode psychosis population, there was a significant variation in the completion rates of assessments. For each chapter, a sample summary will be included with the number of patients that were available for assessments and those that completed the measures relevant to each investigation.

Figure 4.1 Baseline recruitment and retention rates



4.3 Measures

Socio-demographic variables

Data on ethnicity were collected using the Office of National Statistics Classification of Ethnicity (2001). Ethnic groups were merged into 3 categories: black, white and other. The Medical Research Council Socio-demographic Schedule (Mallett, 1997) was used to collect information on current living status (accommodation), relationship and employment status and level of educational achievement. These variables were grouped as following:

1. Living status: living alone or with others
2. Relationship status: single or not single
3. Employment status: employed, unemployed or student
4. Educational level: no qualifications, GCSE/ A and O' Levels and vocational or professional qualifications.

Diagnoses

Operational Criteria (OPCRIT 4)

Diagnoses were made according to DSM-IV criteria (American Psychiatric Association, 2000) using the Operational Criteria (OPCRIT; McGuffin et al., 1991). This was done based on the clinical notes for the month after a patient's first contact with psychiatric services. The first month was used in order to increase reliability of diagnoses across patients who had been in contact with services for various time periods.

Psychiatrists trained in OPCRIT carried out all diagnoses. They scored 10 test diagnoses to ensure inter-rater reliability (Cronbach's Alpha=.95). DSM-IV diagnoses were then pooled to increase simplicity of analysis. These groups were non-affective psychosis (schizophrenia; schizophreniform disorder; delusional disorder; atypical psychosis; psychosis not otherwise specified) and affective psychosis (schizoaffective disorder - depressed type; major depressive episode with psychotic features; schizoaffective disorder – manic type; manic episode with psychotic features).

Psychopathology

Positive and Negative Syndrome Scale (PANSS)

The PANSS (Kay et al, 1987) was used as a measure of current psychopathology. It is a 30-item questionnaire that consists of 3 subscales: positive (7 items), negative (7 items) and general psychopathology (16 items). Each item is scored on a scale of 1 to 7: absent, minimal, mild, moderate, moderate severe, severe and extreme. A score of 4 (moderate) or higher indicates the presence of clinical psychopathology. Each item has specific criteria for each point on the scale to assist with administration and scoring. The measure was completed through interview and collateral information from health-care workers based on the 7 days prior to assessment. PANSS is interpreted as either a total score (range 30-210) or grouped into severity categories of mildly ill (<58), moderately ill (58-74), markedly ill (75-95) and severely ill (>96) (Leucht et al, 2005).

Stressful events

The Brief Life Events Questionnaire (BLEQ)

The BLEQ (Brugha and Cragg, 1990) was used to collect data on significant life events occurring in the six months prior to interview. The questionnaire examines 12 events and patients were asked to indicate whether any of the events had happened to them or not. If yes, then the participant indicated the level of distress caused by that event: very bad, moderately bad or not too bad. The measure yields two scores: a total number of stressful events out of a maximum 12 and a score incorporating the number of stressful events plus the level of distress for each event.

As with other measures, the BLEQ was administered by researchers who read out the questions and invited participants to choose the most suitable response.

Substance use

Tobacco and alcohol

Data were collected on lifetime and current tobacco and alcohol use. Two questions assessed lifetime and current tobacco use, respectively. For information on alcohol use, patients were asked if they had every used alcohol and then to investigate current alcohol use the Alcohol Use Disorders Identification Test (AUDIT; Babor et al, 2001) was used. This measure yields a total score corresponding to levels of alcohol dependency. For parsimonious reasons and to reduce risk of multiple testing, information on tobacco, alcohol and other drug use was limited to current or lifetime use only. As these variables were not primary or secondary outcomes but were used as confounders in later analysis, it was not the objective of this thesis to focus on consumption levels for any of the aforementioned substances. Therefore, the first item of the AUDIT was used to assess current alcohol use. This item indicates how often alcohol has been consumed in the last 12 months (never to 4 or more times per week) and responses were grouped into having used or not having used alcohol in the last year.

Cannabis and other drug use

The Cannabis Experience Questionnaire - Modified Version (CEQ_{mv})

The CEQ_{mv} (DiForti et al, 2009) was used to collect information on cannabis and other drug use (non-prescribed opiates, stimulants, hallucinogens and sedatives). This measure was derived from the original Cannabis Experience Questionnaire (CEQ; Barkus et al 2006), which was developed to assess psychological experiences while under the influence of cannabis as well as immediately after the effects had worn off.

The modified version was expanded to include questions on current and/or past cannabis use, age of first use, frequency of use, type of cannabis preferentially used and context and cost of use. The CEQ_{mv} also includes questions on other non-prescribed drugs both on current and past use including age of first use and frequency of use.

The questionnaire was administered by researchers who read out the questions and invited participants to choose or provide the most suitable response according to lifetime, current use or non-use.

For the description of the sample, patients were classified into the groups summarized in Table 4.1.

Table 4.1 Groups of lifetime and current users and non-users of tobacco, alcohol, cannabis and other drugs

	Tobacco	**Alcohol**	**Cannabis**	**Other drugs**
Lifetime user	Used in the past but not using currently	Used in the past but not in the last year	Used in the past but not in the last year	Used in the past but not using currently
Current user	Current use	Used at least once in the last year	Used at least once in the last year	Current use
Non-user	Never used	Never used	Never used	Never used

Medication compliance

Self-reported medication compliance was assessed using the Composite Measure of Compliance (Kemp et al, 1996). This scale is scored based on assignment to one of the 7 rating points: complete refusal (1), partial refusal (2), reluctant acceptance (3), occasional reluctance (4), passive acceptance (5), moderate participation (6) and active participation (7). Each rating point has specific criteria to assist with administration and scoring, which was carried out by interview from researchers.

Urinary Drug Screen

The Concateno Drug Screen Test Cup (Urine) was used to corroborate self-reported cannabis use. The test is a lateral flow chromatographic immunoassay for the qualitative detection of drugs and drug metabolites in urine for *in vitro* diagnostic use (Tietz, 1986).

A side-by-side comparison conducted using the Concateno Drug Screen Test Cup (Urine) and commercially available rapid drug tests have yielded high accuracy after presumptive positives were confirmed by gas chromatography/ mass spectrometry (GC/MS) (>99% for positive specimens and 99% for negative specimens) (Concateno, 2012).

To test sensitivity a drug-free urine pool was spiked with THC to the concentrations of +/- 50% cut-off. At cut-off (50ng/Ml) the test was able to detect 53% of true positives. This rate was 100% when concentrations reached +50% cut-off. In terms of specificity the test is able to detect 50ng/Ml of positive compounds in urine at 5 minutes (Concateno, 2012).

4.4 Analyses

All analyses were conducted using the Statistical Package for the Social Sciences Version 15 (SPSS 15, 2006). All continuous independent variables were checked for normal distribution using the Kolmogorov-Smirnov test, frequency histograms, Q-Q plots, values of skew and kurtosis. If a variable did not meet the assumptions of parametric tests, non-parametric statistics were used. Where appropriate, variables were split into categorical groupings.

Percentages are presented for all categorical variables and mean scores are presented for all continuous variables except for age, BLEQ, medication compliance, PANSS positive symptoms and PANSS negative symptoms as these had non-normal distributions as follows: The Kolmogorov-Smirnov test showed age, $D(259)=0.136$, $p<.001$, BLEQ, $D(174)=0.174$, $p<.001$, medication compliance, $D(151)=.274$, $p<.001$, PANSS positive symptoms, $D(166)=0.118$, $p<.001$ and PANSS negative symptoms, $D(162)=0.115$, $p<.001$ to have a significant non-normal distribution. Visual investigation of histograms, values of skew and kurtosis, stem-and-leaf plots and Q-Q plots confirmed this observation and so for these variables median scores will be described. Table 4.2 shows the socio-demographic characteristics and table 4.3 the basic clinical characteristics of the baseline sample.

Independent sample t-tests (t) and chi-square tests (χ^2) were used to investigate baseline differences between participants and non-participants as well as current cannabis users and non-users. Based on the observation from the Kolmogorov-Smirnov test above, the Mann-Whitney test (U) was used to describe differences based on age, BLEQ, medication compliance, positive and negative PANSS symptoms. Table 4.4 shows the differences between participants and non-participants based on age, gender and ethnicity and tables 4.5 and 4.6 show the differences between current cannabis users and non- users based on socio-demographic and clinical characteristics, respectively.

4.5 Results

Socio-demographic characteristics of sample

The following observations were made: median age at first presentation to services is late twenties and two-thirds of the sample is male. Half of the patients are of white origin and over a third of black origin and half of the sample holds vocational or professional qualifications. Two-thirds are currently unemployed and live with others and three quarters of the patients are single (Table 4.2).

Table 4.2 Socio-demographic characteristics of baseline sample

Age (n=259)	
Median (IQR)	27 (22-35)
Gender (n=259) (%)	
Male	63.7
Female	36.3
Ethnicity (n=259) (%)	
White	49.8
Black	38.6
Other	11.6
Education level (n=205) (%)	
No qualifications	19.5
GCSE/ A and O' Levels	32.2
Vocational/ professional qualification	48.3
Employment status (n=202) (%)	
Unemployed	63.9
Employed	27.2
Student	8.9
Living status (n=207) (%)	
Alone	33.8
With others	66.2
Relationship status (n=206) (%)	
Single	74.8
Not single	25.2

Clinical characteristics

Almost two-thirds of the patients are diagnosed with non-affective psychosis. The mean total PANSS score falls in the lower end of the moderately ill category and there were no patients in the severely ill group. The median scores on the BLEQ and medication compliance scale indicate a low rate of stressful events and high medication adherence, respectively. There are very high rates of

self-reported alcohol, tobacco and cannabis use with over half the patients reporting current cannabis use (Table 4.3).

Table 4.3 Basic clinical information of baseline sample

Diagnoses (n= 142) (%)	
Non-affective	59.9
Affective	40.1
Total PANSS Scores (n= 154)	
Mean Total (SD)	58.9 (14.6)
PANSS Severity Groups (n= 154) (%)	
Mildly ill	49.4
Moderately ill	35.7
Markedly ill	14.9
Positive PANSS scores (n= 166)	
Median (IQR)	14 (10-18.5)
Negative PANSS scores (n= 162)	
Median (IQR)	14 (10-19)
BLEQ (n= 174)	
Median (IQR)	2 (1-3)
Medication compliance (n= 151)	
Median (IQR)	6 (5-7)
Lifetime cannabis use (n= 201) (%)	
Users	78.1
Non-users	29.1
Current Cannabis use (n= 151) (%)	
Users	55.6
Non-users	44.4

Table 4.3 Basic clinical information of baseline sample (cont.)

Lifetime Tobacco use (n= 200) (%)	
Users	85.5
Non-users	14.5
Current Tobacco use (n= 167) (%)	
Users	77.8
Non-users	22.2
Lifetime Alcohol use (n= 200) (%)	
Users	89.5
Non-users	10.5
Current Alcohol use (n= 166) (%)	
Users	90.4
Non-users	9.6
Other Lifetime Drug use (n= 178) (%)	
Users	53.4
Non-users	46.6
Other Current Drug use (n= 95) (%)	
Users	18.9
Non-users	81.1

Participants vs non-participants

No significant differences were found between participating patients and patients who dropped out at baseline (Table 4.4).

Table 4.4 Differences between participants and non-participants (drop-outs)

	Participants (n= 219)	Non-participants (n= 40)	Test	Sig.
Age			U	0.064
Median (IQR)	26 (22-34)	30.5 (24.25-39.75)		
Gender (%)			χ^2	0.596
Male	64.4	60		
Female	35.6	40		
Ethnicity (%)			χ^2	0.751
White	50.2	47.5		
Non-white	49.8	52.5		

Current self-report cannabis vs non-cannabis users

The following observations were made based on the comparison between current cannabis users and non- users across socio-demographic and clinical data: there were no differences between the two groups on ethnicity, education level and employment or relationship status but cannabis users were more likely to be younger, male and living alone (Table 4.5).

Table 4.5 Differences between current self-reported cannabis and non-cannabis users based on socio-demographic characteristics

	Cannabis users	Non-users	Test	Sig.
Age	**(n= 84)**	**(n= 114)**	U	**0.007**
Median (IQR)	24 (21-31)	28 (22-35)		
Gender (%)	**(n= 84)**	**(n= 114)**	χ^2	**0.001**
Male	78.6	56.1		
Female	21.4	43.9		

Table 4.5 Differences between current self-reported cannabis and non-cannabis users based on socio-demographic characteristics (cont.)

	Cannabis users	Non-users	Test	Sig.
Ethnicity (%)	**(n= 84)**	**(n= 114)**	χ^2	0.268
White	56	44.7		
Black	33.3	39.5		
Other	10.7	15.8		
Education level (%)	**(n= 81)**	**(n= 108)**	χ^2	0.166
No qualifications	24.7	13.9		
GCSE/ A and O' Levels	29.6	33.3		
Vocational/ professional qualification	45.7	52.8		
Employment status (%)	**(n= 79)**	**(n= 107)**	χ^2	0.240
Unemployed	70.9	58.9		
Employed	7.6	10.3		
Student	21.5	30.8		
Living status (%)	**(n= 81)**	**(n= 109)**	χ^2	**0.004**
Alone	44.4	24.8		
With others	55.6	75.2		
Relationship status (%)	**(n= 80)**	**(n= 109)**	χ^2	0.357
Single	77.5	71.6		
Not single	22.5	28.4		

There were no differences between the two groups on diagnoses, assignment to PANSS severity group or medication compliance. Cannabis users had a higher total PANSS score than non-users as well as a higher score on the positive PANSS subscale and reported more stressful life events in the 6 months prior to interview. Cannabis users were also more likely to report lifetime and current tobacco, alcohol and other drug use than non- users (Table 4.6).

A total of 88 baseline urine drug screens were performed to corroborate current cannabis use (Table 4.6). There was a fair agreement (Cohen's

kappa=0.37) (Landis and Koch, 1977) between participants' reports and urinalysis. Based on findings by Martin et al (1988), it was expected that the agreement would be higher but this is very likely due to the high number of cannabis users who produced negative screens. As the aim at baseline was to capture occasional as well as regular and recent cannabis use (at least once in the last year), it is expected that self-reported use will not always correspond to positive samples. It is anticipated that this agreement will be higher at 3- and 12-month follow-ups as criteria for cannabis use are not dependent on a strict time frame. Two of the 42 self-reported non-users produced UDS results positive for cannabis. It is most likely that these present false negative results based on Colcateno sensitivity levels at 97%. Therefore, these two patients will continue to be treated as non-users for the purposes of analysis.

Table 4.6 Differences between self-reported current cannabis users and non-users based on clinical characteristics

	Cannabis users	**Non-users**	**Test**	**Sig.**
Diagnosis (%)	**(n= 57)**	**(n= 74)**	χ^2	0.893
Non-affective	59.6	60.8		
Affective	40.4	39.2		
Total PANSS scores	**(n= 62)**	**(n= 86)**	*t*	**0.017**
Mean Total (SD)	62.56 (15)	56.77 (14.1)		
PANSS Severity Groups (%)	**(n= 62)**	**(n= 86)**	χ^2	0.065
Mildly ill	38.7	54.7		
Moderately ill	38.7	34.9		
Markedly ill	22.6	10.4		
Positive PANSS scores	**(n= 71)**	**(n= 88)**	U	**0.004**
Median (IQR)	15(11-21)	13(8-16.75)		
Negative PANSS scores	**(n= 67)**	**(n= 88)**	U	0.258
Median (IQR)	15 (10-20)	13(9.25-17)		

Table 4.6 Differences between current self-reported cannabis users and non-users based on clinical characteristics (cont.)

	Cannabis users	Non-users	Test	Sig.
BLEQ	**(n=72)**	**(n= 97)**	U	**0.001**
Median (IQR)	3 (1-4)	2 (1-3)		
Medication Compliance	**(n=61)**	**(n=89)**	U	0.068
Median (IQR)	6 (5-7)	7 (5-7)		
Lifetime Tobacco use (%)	**(n= 82)**	**(n= 112)**	χ^2	**<0.001**
User	98.8	75		
Non-user	1.2	25		
Current Tobacco use (%)	**(n= 81)**	**(n= 81)**	χ^2	**<0.001**
User	92.6	64.2		
Non-user	7.4	35.8		
Lifetime Alcohol use (%)	**(n= 81)**	**(n= 112)**	χ^2	**0.021**
User	96.3	86.6		
Non-user	3.7	13.4		
Current Alcohol use (%)	**(n= 79)**	**(n= 104)**	χ^2	**0.010**
User	89.9	75		
Non-user	10.1	25		
Other Lifetime Drug use (%)	**(n= 82)**	**(n= 97)**	χ^2	**<0.001**
User	72	37.1		
Non-user	28	62.9		
Other Current Drug use (%)	**(n= 82)**	**(n= 97)**	χ^2	**0.004**
User	17.1	4.1		
Non-user	82.9	95.9		
Urinary Drug Screen (%)	**(n= 46)**	**(n=42)**	Kappa	<0.001
Positive	40.5	4.3		
Negative	59.5	95.7		

Current cannabis vs non-cannabis users based on UDS results

There were no differences between current cannabis users and non-users according to UDS results in baseline positive and total PANSS scores (table 4.7).

Table 4.7 Differences between current cannabis users and non-users based on UDS results (cont.)

	Cannabis users	**Non-users**	**Test**	**Sig.**
Total PANSS scores	**(n= 14)**	**(n= 57)**	*t*	0.210
Mean Total (SD)	56.75 (12)	61.29 (12)		
Positive PANSS scores	**(n= 16)**	**(n= 58)**	U	0.536
Median (IQR)	15.5 (11-19.5)	15 (10-18)		

4.6 Discussion

This chapter reported the basic socio-demographic and clinical characteristics of the baseline sample and a comparison of participants and non-participants as well current cannabis users and non-users on variables of interest.

All participants

Age at first presentation to services, employment, living and relationship status are consistent with data from other first-episode studies in London and the rest of the U.K. (Morgan et al, 2005; Hutton et al, 1998; Morrison et al, 2012) although in our sample a larger percentage of patients were of white ethnicity compared to black. Also, in our study half of the patients held vocational or professional qualifications, which is not consistent with the findings of the AESOP study (Morgan et al, 2005), but this might be due to grouping of educational levels into different categories between the AESOP and present study. The ratio of male to female participants in this study was consistent with data in the aforementioned first-episode studies in London and the U.K. Similarly in a study by Kirkbride et al (2006) the risk for all psychotic disorders, with the exception of affective psychosis, after controlling for age, study centre and ethnicity, was greater for men than women. In the general population, cannabis users who come in contact with treatment services tend to be younger, male and in mainstream education but living with family or other relatives rather than alone (National Treatment Agency for Substance Misuse, 2012).

There were very high rates of self-reported alcohol, tobacco and cannabis use with over half the patients reporting current cannabis use. Previous studies on recent-onset psychosis and related disorders have reported similarly high rates (Addington and Addington, 2007; Hinton et al, 2007; Degenhardt et al, 2007).

Psychopathology levels were low with complete absence of patients scoring on the severe end of the PANSS spectrum and this might appear surprising considering the nature of a first-episode population. For ethical reasons patients were only approached for consent after consulting with assigned health-care staff. If they didn't judge the patient to be well enough to be provided with information about the study, this was postponed until permission was given. It is only natural that within this time patients' mental

health improved. Also, the high levels of self-reported medication adherence might partly explain the moderate levels of psychopathology in this sample.

Cannabis vs non-cannabis users

As previously observed (Addington and Addington, 2007; Linszen et al, 1994), cannabis users were more likely to be younger and male than non-users.

Cannabis users also showed higher rates of lifetime and current tobacco, alcohol and other drug use than non-users. Degenhardt et al (2007) reported that over two-thirds of the cannabis users in their study had used tobacco and alcohol in the last month but no research has compared cannabis users and non-users on other drug use and it is the aim of this thesis to examine differences between the two groups at each time point.

Previous comparisons between cannabis users and non-users on clinical measures have revealed mixed findings, which are apparent in the current study as well. Some studies have found differences in baseline psychopathology with cannabis users rating higher (Addington and Addington, 2007) but others have reported similar scores in the two groups (e.g. Stirling et al, 2005). In this study, cannabis users had a higher total and positive, but not negative, PANSS score and reported more stressful life events than non-users. These will be statistically controlled for in later analyses, as will alcohol, tobacco and other drug use since there were significant differences between the two groups on these measures.

Self-reported cannabis use has been shown to be more accurate than collateral reports (Martin et al, 1988; Wolford et al, 1999; Selten et al, 2002) and therefore we did not expect a significant difference on psychopathology outcomes between users with positive and negative UDS. However, it is most likely that in a sample of largely hospitalised patients access to cannabis was limited at the time of assessments and self-reported use in the last year was more accurately associated with symptomatology. This is consistent with findings from longitudinal studies that have found that improvement in symptoms after cannabis use cessation can be seen more clearly in the long rather than short term (Gonzáles-Pinto et al, 2011).

4.7 Summary

The sample characteristics observed at baseline were similar to other studies on recent-onset psychosis with regards to the ratio of male to female participants, relationship, employment and living status. A larger percentage of patients from white rather than black ethnicity participated in this study and half of the patients held vocational or professional qualifications. No differences were found between those who were available for baseline assessments and those who dropped out shortly after consent. Cannabis users were more likely to be younger and male and reported higher rates of lifetime and current tobacco, alcohol and other drug use. They also scored higher on the total and positive PANSS scales and reported more stressful events than non-users. In the next chapter the effects of cannabis use at 12 months on total and positive symptom severity as well as its association with other drug use at the 3 time-points will be examined.

Chapter 5 – Association of cannabis use with symptom severity at 12 months and other drug use at baseline, 3 months and 12 months

5.1 Synopsis

The systematic review on the consequences of cannabis use on the course of psychosis showed that the effects of persistent use have been inconclusive (Chapter 2; section 2.2). Some studies have found that continuous cannabis use is associated with higher relapse rates and more positive symptoms but not negative symptoms. Variations in diagnostic criteria for psychosis, small sample sizes and lack of adequate adjustment for confounders are some of the methodological limitations. No research has examined the relationship between cannabis use and other drug use in patients with psychosis.

This chapter aims to first assess the effects of 12-month cannabis use on symptom severity (total and positive PANSS scores) while controlling for potential baseline confounders and second to examine the association between cannabis and other drug use at 3 time points; baseline, 3 months and 12 months. No significant association was observed between cannabis use and total PANSS scores at 12 months and total PANSS scores at baseline were the only predictors of total PANSS scores at 12 months. Cannabis use at 12 months, total PANSS scores and current tobacco use at baseline were associated with 12-month positive PANSS symptoms but in a multivariate analysis only the association between baseline total PANSS scores and 12-month positive PANSS scores remained significant. Cannabis users were more likely than non-users to use other drugs at baseline and 3 months but this difference was not detected at 12 months.

These findings contribute to the evidence base that cannabis use does not appear to worsen prognosis following the onset of psychosis. Reasons for these negative findings are examined in this chapter. The relationship of cannabis with other drug use will be discussed within the context of this project as well as findings from general population studies as previous psychiatric research has not investigated this association.

5.2 Hypotheses

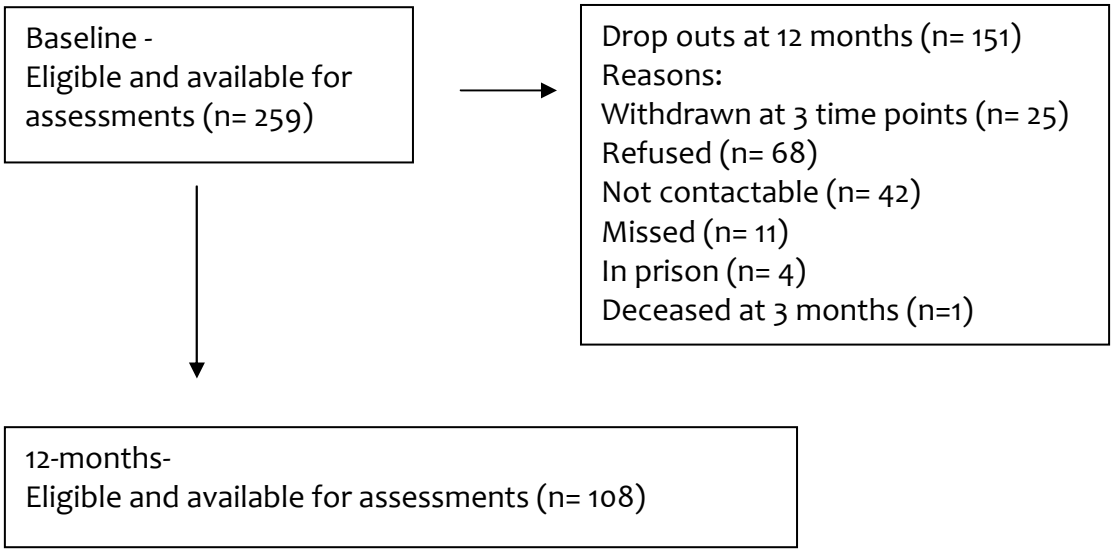
1. Patients who use cannabis at 12 months will have higher total symptom severity than those who are not current users or have never used cannabis.
2. Patients who use cannabis at 12 months will have more positive symptoms than those who are not current users or have never used cannabis.
3. At each time point, patients who use cannabis will be more likely to use other drugs than those who are not current users or have never used cannabis.

5.3 Sample selection

Cannabis use and psychotic symptoms at 12 months

Of the 259 patients available for assessment at baseline, 151 dropped out at 12-month follow-up time leaving a sample of 108 patients available for assessments. A summary of the retention rates and reasons for drop out at 12 months are summarized in Figure 5.1.

Figure 5.1 Retention rates at 12 months

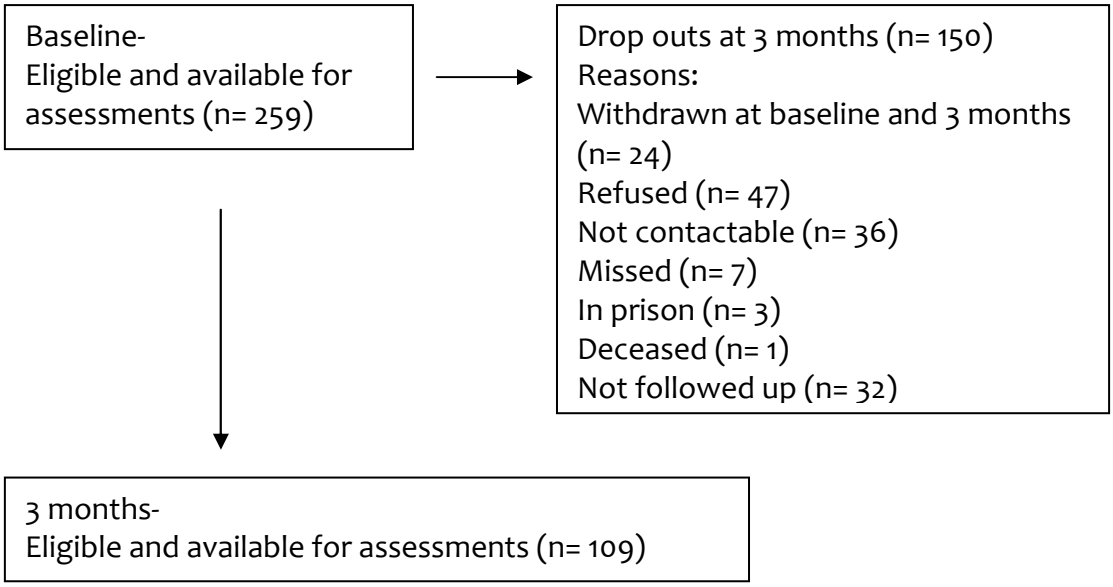


Cannabis and other drug use at baseline, 3 months and 12months

Due to the high rate of attrition at follow-up points, in October 2010 3-month follow-up assessments were stopped to focus resources on 12-month follow-up assessments. Thirty-two patients were therefore not assessed at 3 months. At 3 months, 109 of the 259 patients were available for assessments. A

summary of retention rates at 3 months is presented in Figure 5.2. At baseline 219 patients were available for assessments (Chapter 4; Figure 4.1) and 108 patients were available at 12 months (Figure 5.1). Completion rates of measures used in the analyses vary from these figures and are indicated in the respective results sections.

Figure 5.2 Retention rates at 3 months



5.4 Measures

Symptom severity was assessed using the PANSS. Cannabis and other drug use were established through the CEQ_{mv} and stressful events were assessed by the BLEQ. Questions on lifetime and current tobacco, alcohol and other drug use were used to group patients into users and non-users. Urinalysis was also performed at 3 and 12 months. Details of these measures as well as instruments used to collect information on age and gender have been described in Chapter 4 (section 4.2).

5.5 Analyses

Comparison between completers and non-completers

Chi-square tests, independent sample t-tests and Mann-Whitney tests were used to assess differences on gender, age, baseline cannabis use and baseline total and positive PANSS scores between completers and non-completers of 12-month total PANSS scale. These tests were also used to

examine differences between patients who had completed the 12-month positive PANSS scales and to investigate differences between patients with information on other drug use and those with missing data.

Cannabis use and total PANSS scores at 12 months

A univariate and multivariate linear regression approach was used to address the relationship between cannabis use and total PANSS scores at 12 months. The potential confounders were age, gender and baseline total PANSS scores, positive PANSS scores, BLEQ scores, lifetime and current tobacco use, lifetime and current alcohol use and other lifetime and current drug use.

First, unadjusted analyses were conducted to describe the data. Using visual inspection of the data and formal statistical tests, the normality of the total PANSS scores distribution in cannabis users and non-users at 12 months was investigated. The Mann-Whitney test and Spearman's correlation (r_s) were used to assess each potential covariate and differences in or associations with total PANSS scores at 12 months respectively.

Variables were entered into the regression model starting with the main explanatory variable, cannabis use at 12 months. Each variable was then entered in sequence of importance based on significance levels and effect size from baseline comparisons between cannabis users and non-users. If a variable significantly contributed to the model, it was retained and this process was applied to all subsequent variables to assess whether they contributed to the model. If a variable showed no significant association with 12-month total PANSS scores, after controlling for variables already in the model, it was removed. In the final model cannabis use was retained regardless of significant contribution, as it was the main explanatory variable of interest.

Cannabis use and positive PANSS scores at 12 months

A univariate and multivariate regression approach was used to address the relationship between cannabis use and positive PANSS scores at 12 months. The potential confounders were age, gender, baseline total PANSS scores, positive PANSS scores, BLEQ scores, lifetime and current tobacco use, lifetime and current alcohol use and other lifetime and current drug use.

First, unadjusted analyses were conducted to describe the data. Using visual inspection of the data and formal statistical tests, the normality of the positive PANSS scores distribution in cannabis users and non-users at 12 months was investigated. The Mann-Whitney test and Spearman's correlation (r_s) were used to assess each potential covariate and differences in or associations with positive PANSS scores at 12 months respectively.

Variables were entered into the regression model starting with the main explanatory variable, cannabis use at 12 months. The aforementioned method of building the regression model was followed. In the final model cannabis use was retained regardless of significant contribution, as it was the main explanatory variable of interest.

Association between cannabis use and other drug use at baseline, 3 months and 12 months

A logistic regression approach was used to test whether cannabis use at each time point was associated with other drug use. Potential confounders were age, gender, baseline total PANSS scores, positive PANSS scores and BLEQ scores. As with the linear regression model, variables were entered based on significance level and effect size from baseline comparisons between cannabis users and non-users. If a variable significantly contributed to the model, it was retained and this was repeated for every subsequent variable. Cannabis use was retained in the model regardless of significant contribution, as it was the main predictor of interest.

Unadjusted analysis was carried out to provide an overall description of the data. The Mann-Whitney test, independent samples t-test, chi-square test and Fisher's exact test were used to assess each potential covariate and differences in or associations with other drug use at each time point.

5.6 Results

Completers vs non-completers of 12-month total and positive PANSS scale

Comparisons between completers and non-completers of 12-month total PANSS found no differences in age or gender but showed that patients who did not complete the 12-month total PANSS reported significantly higher baseline total PANSS scores (*M*=61.2, *SE*=1.8) than those who completed total PANSS assessment at 12 months (*M*=56.2, *SE*=1.4; *t*(152)=2.11, p=0.037). Results also showed that patients who did not complete the 12-month total PANSS reported significantly higher baseline positive PANSS symptoms than those who completed the assessment (U=2748.5, p=0.040) (Table 5.1).

Table 5.1 Differences between completers and non-completers of 12-month total PANSS scale

	Completers	**Non-completers**	**Test**	**Sig**
Gender (%)	**(n=99)**	**(n =160)**	χ^2	0.060
Male	56.6	68.1		
Female	43.4	31.9		
Age	**(n=99)**	**(n=160)**	U	0.969
Median (IQR)	27(23-35)	27.5 (21.25-36.75)		
Baseline Cannabis use (%)	**(n=79)**	**(n=119)**	χ^2	0.656
Users	40.5	43.7		
Non-users	59.5	56.3		
Baseline PANSS scores	**(n=71)**	**(n=83)**	t	**0.037**
Mean (SD)	56.2(12)	61.2(16)		
Baseline PANSS positive scores	**(n=75)**	**(n=90)**	U	**0.040**
Median (IQR)	12(9-16)	15(10-20)		

Comparisons between completers and non-completers of 12-month positive PANSS scale revealed no differences in age, baseline total or positive PANSS scores but male participants were more likely to complete the 12-month positive PANSS scale ($\chi^2(1)=4.5$, p=0.034) than female participants (Table 5.2).

Table 5.2 Differences between completers and non-completers of 12-month positive PANSS scale

	Completers	Non-completers	Test	Sig
Gender (%)	**(n=94)**	**(n=165)**	χ^2	**0.034**
Male	55.3	68.5		
Female	44.7	31.5		
Age	**(n=94)**	**(n=165)**	U	0.851
Median (IQR)	26.5(23-34.25)	28(22-37)		
Baseline Cannabis use (%)	**(n=80)**	**(n=118)**	χ^2	0.783
Users	41.3	43.2		
Non-users	58.7	56.8		
Baseline PANSS scores	**(n=74)**	**(n=91)**	t	0.237
Mean (SD)	57.4	60.2		
Baseline PANSS positive scores	**(n=74)**	**(n=91)**	U	0.206
Median (IQR)	13(10-16.25)	14(10-20)		

Completers vs non-completers of other drug use at baseline, 3 months and 12 months

With regards to other drug use, comparisons between completers and non-completers showed one significant difference. At baseline, patients without available data on other drug use reported higher positive PANSS scores than those whose data were available (U=728.5, p=0.024). No other differences were observed at any of the 3 time-points (Table 5.3).

Table 5.3 Comparison between completers and non-completers of information on other drug use at 3 time points

	Completers	Non-completers	Test	Sig
BASELINE				
Gender (%)	**(n=181)**	**(n=78)**	χ^2	0.448
Male	65.2	60.3		
Female	34.8	39.7		
Age	**(n=181)**	**(n=78)**	U	0.368
Median (IQR)	26(22-35)	29(23-36.25)		
Baseline total PANSS scores	**(n=140)**	**(n=14)**	t	0.159
Mean (SD)	59.4(14.8)	53.6(12.4)		
Baseline positive PANSS scores	**(n=150)**	**(n=15)**	U	**0.024**
Median (IQR)	14(10-19)	19(7-13)		
3- MONTH FOLLOW-UP				
Gender (%)	**(n=83)**	**(n=176)**	χ^2	0.756
Male	65.1	63.1		
Female	34.9	36.9		
Age	**(n=83)**	**(n=176)**	U	0.779
Median (IQR)	27(22-35)	27.5(22-36.75)		
Baseline total PANSS scores	**(N=64)**	**(N=90)**	t	0.066
Mean (SD)	56.3(13.9)	60.7(15)		
Baseline positive PANSS scores	**(N=70)**	**(N=95)**	U	0.287
Median (IQR)	14(9-17)	14(10-19)		
12-MONTH FOLLOW-UP				
Gender (%)	**(n=76)**	**(n=183)**	χ^2	0.493
Male	60.5	65		
Female	39.5	35		
Age	**(n=76)**	**(n=183)**	U	0.694
Median (IQR)	28(23-34)	27(22-36)		

Table 5.3 Comparison between completers and non-completers of information on other drug use at 3 time points (cont.)

	Completers	Non-completers	Test	Sig
Baseline total PANSS scores	**(n=53)**	**(n=101)**	t	0.389
Mean (SD)	57.5(12.8)	59.6(15.5)		
Baseline positive PANSS scores	**(n=59)**	**(n=106)**	U	0.336
Median (IQR)	13(10-18)	14.5(10-19)		

Cannabis use and total PANSS scores at 12 months

The Kolmogorov-Smirnov test showed total PANSS scores in the cannabis users to be normally distributed, $D(29)=.092$, p=.20 and total PANSS scores in the non-users to have a non-normal distribution, $D(61)=.116$, p=.04. Visual investigation of the data confirmed this observation and so unadjusted results were attained through non-parametric procedures.

The Mann-Whitney test was used to examine the differences in 12-month total PANSS scores between cannabis and non-cannabis users, male and female participants, baseline current and lifetime tobacco users and non-users, lifetime and current alcohol users and non-users and other lifetime and current drug users and non-users. Significant gender differences were observed. Male patients reported higher symptom severity (Mdn=51.5) at 12 months than female patients (Mdn=42), $U=882$, p=.023. No other comparisons yielded significant findings (Table 5.4).

Spearman's correlations were used to assess the association between age, baseline total PANSS scores, positive PANSS scores, BLEQ scores and 12-month total PANSS scores at two-tailed significance. A positive relationship was found between baseline total PANSS scores and 12-month total PANSS scores ($r=0.28$, p=0.019). No other significant relationships were observed (Table 5.5).

Table 5.4 Unadjusted effects on 12-month total PANSS scores by main explanatory variable and potential confounders

	12-month PANSS scores Median (IQR)	Test	Sig
Cannabis use at 12 months		U	0.086
Users (n=25)	54(43-62)		
Non-users (n=61)	46(36-60)		
Gender		U	**0.023**
Male (n=56)	51.5(38.25-61.75)		
Female (n=43)	42(32-50)		
Baseline Lifetime Tobacco use		U	0.592
Users (n=66)	46(35-62.5)		
Non-users (n=15)	44(32-60)		
Baseline Current Tobacco use		U	0.118
Users (n=44)	48(37.5-64)		
Non-users (n=35)	42(32-60)		
Baseline Lifetime Alcohol use		U	0.922
Users (n=72)	45.5(35-63.5)		
Non-users (n=9)	47(42.5-56)		
Baseline Current Alcohol use		U	0.174
Users (n=60)	43.5(35-58.75)		
Non-users (n=17)	52(42.5-63.5)		
Baseline Other Lifetime Drug use		U	0.908
Users (n=37)	45(35-60)		
Non-users (n=36)	56.5(35.25-63.75)		
Baseline Other Current Drug use		U	0.600
Users (n=5)	36(33.5-61)		
Non-users (n=68)	46(35-62.25)		

Table 5.5 Spearman's correlation coefficients between potential confounders and 12-month total PANSS scores

	12-month PANSS scores	Sig
Baseline total PANSS scores	0.28	**0.019**
Baseline positive PANSS scores	0.04	0.735
Baseline BLEQ	0.08	0.471
Age	-0.53	0.601

A univariate linear regression was used to assess the association between cannabis use (dependent variable) and total PANSS scores (independent variable) at 12 months. Although results from the unadjusted tests showed significant findings only for gender and baseline total PANSS scores, it was decided to further test all dependent variables (baseline total and positive PANSS scores, age, gender, baseline BLEQ, baseline lifetime and current alcohol use, baseline other lifetime and current drug use and baseline lifetime and current tobacco use) in separate regressions as previous research has shown these covariates attenuate the level to which cannabis use is associated with symptom severity. The only variable that was significantly associated with total symptom severity at 12 months was baseline total PANSS scores ($F(1,69)= 5.09$, $p=0.027$). This variable predicted 6.9% of the variance in 12-month total PANSS scores. The main dependent variable, cannabis use at 12 months, was not significantly associated with 12-month total PANSS scores at the 5% level, but was retained in the model anyway. In the final model, baseline total PANSS scores were entered together with cannabis use at 12 months and remained a significant predictor of 12-month total PANSS scores. Although cannabis use was not associated with 12-month total PANSS scores on its own ($p=0.081$), adjusting for baseline total PANSS scores improved the significance level ($p=0.071$). The final model ($n=67$) accounted for 11.7% of the variance in 12-month total PANSS scores ($F(2, 64)= 4.2$, $p=0.035$) (Table 5.6). For an average one-point increase in baseline total PANSS scores, 12-month total PANSS scores increased by 0.38 points when baseline total PANSS scores were the only predictor. When added to the final model together

with 12-month cannabis use, the increase was attenuated to 0.32 but remained significant.

The distribution of the residuals versus predicted value was examined for linearity and homoscedasticity; the autocorrelation plot was examined for independence and the normal probability plot was examined for normality. No violations of the above assumptions of linear regression were found.

Table 5.6 Linear regression model assessing predictors of 12-month total PANSS scores

	B	95% CI	Sig
Univariate analysis			
Cannabis use at 12 months	5.60	-0.70 – 11.90	0.081
Baseline total PANSS scores	0.38	0.04 – 0.72	**0.027**
Baseline positive PANSS scores	0.30	-0.71 – 0.77	0.935
Age	-0.05	35 – 60	0.787
Gender	-7.14	-14.80 – 0.51	0.067
Baseline BLEQ	0.64	-1.56 – 2.84	0.565
Baseline Lifetime Alcohol use	3.14	-8.79 – 16.06	0.602
Baseline Current Alcohol use	-4.08	-13.31 – 5.14	0.381
Baseline Other Lifetime Drug use	1.16	-6.53 – 8.85	0.764
Baseline Other Current Drug use	-2.84	-18.06 – 12.38	0.711
Baseline Lifetime Tobacco use	3.59	-6.04 – 13.22	0.461
Baseline Current Tobacco use	5.86	-1.76 – 13.48	0.130
Multivariate analysis (final model)			
Cannabis use at 12 months	7.07	-0.62 - 14.75	0.071
Baseline total PANSS scores	0.32	0.02 - 0.61	**0.035**

Cannabis use and positive PANSS scores at 12 months

The Kolmogorov-Smirnov test showed positive PANSS scores in the cannabis users to be normally distributed, $D(29)=.145$, $p=0.123$ and positive PANSS scores in the non-users to have a non-normal distribution, $D(64)=.210$,

p<0.001. Visual investigation of the data confirmed this observation and so unadjusted results were attained through non-parametric procedures.

The Mann-Whitney test was used to examine the differences in 12-month positive PANSS scores between cannabis and non-cannabis users, male and female participants, baseline current and lifetime tobacco users and non-users, lifetime and current alcohol users and non-users and other lifetime and current drug users and non-users. Cannabis users reported higher positive PANSS scores (Mdn=11) than non-users (Mdn=9; U=682, p=0.039). No other significant differences were observed (Table 5.7).

Spearman's correlations were used to assess the association between age, baseline total PANSS scores, positive PANSS scores, BLEQ scores and 12-month positive PANSS scores at two-tailed significance. No significant relationships were observed (Table 5.8).

Table 5.7 Unadjusted effects on 12-month positive PANSS scores by main explanatory variable and potential confounders

	12-month positive PANSS scores Median (IQR)	**Test**	**Sig**
Cannabis use at 12 months		U	**0.039**
Users (n=29)	11(8-15)		
Non-users (n=64)	9(7-13)		
Gender		U	0.833
Male (n=52)	10(7.25-14)		
Female (n=42)	9.5(7-15)		
Baseline Lifetime Tobacco use		U	0.172
Users (n=68)	10(7.25-15)		
Non-users (n=15)	9(7-10)		
Baseline Current Tobacco use		U	0.052
Users (n=46)	10(8-15)		
Non-users (n=33)	9(7-11.5)		

Table 5.7 Unadjusted effects on 12-month positive PANSS scores by main explanatory variable and potential confounders (cont.)

	12-month positive PANSS scores Median (IQR)	Test	Sig
Baseline Lifetime Alcohol use		U	0.719
Users (n=73)	10(7-14.5)		
Non-users (n=8)	9.5(9-10)		
Baseline Current Alcohol use		U	0.862
Users (n=60)	9(7-14.75)		
Non-users (n=17)	10(8.5-11)		
Baseline Other Lifetime Drug use		U	0.529
Users (n=38)	9.5(7-13.25)		
Non-users (n=36)	10(7.25-15)		
Baseline Other Current Drug use		U	0.527
Users (n=5)	7(7-16.5)		
Non-users (n=69)	10(8-14)		

Table 5.8 Spearman's correlation coefficients between potential confounders and 12-month positive PANSS scores

	12-month positive PANSS scores	Sig
Baseline total PANSS scores	0.19	0.112
Baseline positive PANSS scores	0.23	0.052
Baseline BLEQ	0.08	0.471
Age	-0.10	0.351

A univariate linear regression was used to assess the relationship between cannabis use (dependent variable) and positive PANSS scores (independent variable) at 12 months. Although results from the unadjusted tests showed significant findings only for cannabis use, it was decided to further test all dependent variables (baseline total and positive PANSS scores, age, gender, baseline BLEQ, baseline lifetime and current alcohol use, baseline other lifetime and current drug use and baseline lifetime and current tobacco use) in separate

regressions as previous research has shown these covariates attenuate the level to which cannabis use predicts positive symptom severity. The variables that were significantly associated with 12-month positive PANSS score were cannabis use at 12 months ($F(1,91)= 5.34$, $p=0.023$), baseline total PANSS scores ($F(1,67)= 4.74$, $p=0.033$) and baseline current tobacco use ($F(1,77)= 4.48$, $p=0.038$). These variables predicted 5.5%, 6.6% and 5.5% of the variance in 12-month positive PANSS scores, respectively. In the final model, baseline total PANSS scores and baseline current tobacco use were added to cannabis use at 12 months. The only variable that remained a significant predictor of 12-month positive PANSS symptoms was baseline total PANSS scores. The final model (N=66) accounted for 14% of the variance in 12-month positive PANSS scores ($F(3, 62)= 3.35$, $p=0.025$) (Table 5.9). For an average one-point increase in baseline total PANSS scores, 12-month positive PANSS scores increased by 0.10 points when controlling for cannabis use at 12 months and baseline current tobacco use.

The distribution of the residuals versus predicted value was examined for linearity and homoscedasticity; the autocorrelation plot was examined for independence and the normal probability plot was examined for normality. No violations of the above assumptions of linear regression were found.

Table 5.9 Linear regression model assessing predictors of 12-month positive PANSS scores

	B	95% CI	Sig
Univariate analysis			
Cannabis use at 12 months	2.20	0.31 – 4.10	**0.023**
Baseline total PANSS scores	0.89	0.01 – 0.17	**0.033**
Baseline positive PANSS scores	0.16	-0.02 – 0.33	0.085
Age	-0.02	-0.11 – 0.08	0.734
Gender	-034	-2.14 – 1.45	0.707
Baseline BLEQ	0.21	-0.34 – 0.76	0.444
Baseline Lifetime Alcohol use	1.71	-1.47 – 4.88	0.288
Baseline Current Alcohol use	1.37	-0.98 – 3.72	0.250
Baseline Other Lifetime Drug use	-0.82	-2.86 – 1.22	0.426
Baseline Other Current Drug use	-0.36	-4.44 – 3.72	0.861
Baseline Lifetime Tobacco use	2.34	-0.21 – 4.88	0.071
Baseline Current Tobacco use	2.03	0.12 – 3.95	**0.038**
Multivariate analysis (final model)			
Cannabis use at 12 months	1.86	-0.63 – 4.36	0.140
Baseline total PANSS scores	0.10	0.01 – 0.17	**0.041**
Baseline Current Tobacco use	1.23	-1.05 – 3.52	0.285

Repeated-measures analysis

A repeated measures analysis was not feasible because the sample size of patients with total PANNS scores at both time points would have been small in one of the cells (n=3 for non-cannabis users at baseline who reported cannabis use at 12 months), which does not provide adequate power to detect an interaction or the minimum sample size to obtain a stable model. As an alternative a univariate regression was used to test the differences between the 4 cannabis groups (baseline and 12-month use/ baseline use and 12-month non-use/ baseline and 12-month non-use/ baseline non-use and 12-month use). Results confirmed the findings from the existing regression: cannabis use was not a predictor of total PANSS scores at 12 months ($F(3,62=1.34, p=0.269$) and only

baseline total PANSS scores remained a significant predictor of 12-month total PANSS scores (B=0.322, p=0.035). It is apparent that additional analysis within the limitations of the sample size does not produce different results and is therefore not necessary.

Cannabis use and other drug use at baseline, 3 months and 12 months

At baseline, the chi-square test was used to investigate gender and cannabis use differences between other drug users and non-users and the Fisher's exact test was used at 3 and 12 months. The Mann-Whitney test was used to explore differences in age, baseline positive PANSS scores and BLEQ scores between other drug users and non-users at the three time-points and an independent-samples t-test was performed to examine differences in baseline total PANSS scores between the two groups at each time point.

At baseline, there was a significant association between cannabis use and other drug use ($\chi^2(1)=8.24$, p=0.004). Patients who used cannabis were 5 times more likely to also use other drugs than non-users. No other significant findings were observed (Table 5.10).

At 3 months there was still a significant association between cannabis and other drug use (Fisher's exact, p=0.003) (Table 5.11) but this significant relationship was not observed at 12 months (Table 5.12). No other significant relationships were found.

A logistic regression model was performed only for baseline data, as there were less than 10 other drug users at 3 and 12 months, which violated the assumptions for a logistic regression.

Table 5.10 Unadjusted effects on other drug use at baseline by main explanatory variable and potential confounders

	Other drug users	**Non-users**	**Test**	**Sig**
Gender (%)	**(n=18)**	**(n=163)**	χ^2	0.089
Male	83.3	63.2		
Female	16.7	36.8		
Age	**(n=18)**	**(n=163)**	U	0.368
Median (IQR)	29(23-38.8)	26(21-35)		

Table 5.10 Unadjusted effects on other drug use at baseline by main explanatory variable and potential confounders (cont.)

	Other drug users	Non-users	Test	Sig
Cannabis use at baseline (%)	**(n=18)**	**(n=168)**	χ^2	**0.004**
Users	77.8	42.2		
Non-users	22.2	57.8		
Baseline BLEQ	**(n=15)**	**(n=141)**	U	0.147
Median (IQR)	3(1-4)	2(1-3)		
Baseline total PANSS scores	**(n=15)**	**(n=125)**	t	0.835
Mean (SD)	58.7(14)	59.9(14.9)		
Baseline positive PANSS scores	**(n=16)**	**(n=134)**	U	0.848
Median (IQR)	14(11-20.75)	14.50(10-19)		

Table 5.11 Unadjusted effects on other drug use at 3 months by main explanatory variable and potential confounders

	Other drug users	Non-users	Test	Sig
Gender (%)	**(n=9)**	**(n=74)**	Fisher's	0.484
Male	77.8	63.5		
Female	22.2	36.5		
Age	**(n=9)**	**(n=74)**	U	0.212
Median (IQR)	24(21-28)	28(22-35)		
Cannabis use at 3 months (%)	**(n=9)**	**(n=74)**	Fisher's	**0.003**
Users	77.8	25.7		
Non-users	22.2	74.3		
Baseline BLEQ	**(n=9)**	**(n=62)**	U	0.354
Median (IQR)	3(1-4.5)	2(1-3)		
Baseline total PANSS scores	**(n=7)**	**(n=57)**	t	0.320
Mean (SD)	61.3(16.5)	55.7(13.6)		

Table 5.11 Unadjusted effects on other drug use at 3 months by main explanatory variable and potential confounders (cont.)

	Other drug users	Non-users	Test	Sig
Baseline positive PANSS scores	**(n=8)**	**(n=62)**	U	0.270
Median (IQR)	14(10.25-23)	13.5(8-16.25)		

Table 5.12 Unadjusted effects on other drug use at 12 months by main explanatory variable and potential confounders

	Other drug users	Non-users	Test	Sig
Gender (%)	**(n=7)**	**(n=69)**	Fisher's	1.000
Male	57.1	60.9		
Female	42.9	39.1		
Age	**(n=7)**	**(n=69)**	U	0.155
Median (IQR)	29(24-48)	27(22.5-34)		
Cannabis use at 12 months (%)	**(n=7)**	**(n=68)**	Fisher's	0.419
Users	57.1	36.8		
Non-users	42.9	63.2		
Baseline BLEQ	**(n=5)**	**(n=57)**	U	0.527
Median (IQR)	2(1.5-4)	2(1-3)		
Baseline total PANSS scores	**(n=5)**	**(n=48)**	t	0.074
Mean (SD)	67.2(4.6)	56.5(13)		
Baseline positive PANSS scores	**(n=5)**	**(n=54)**	U	0.926
Median (IQR)	11(9.5-19.5)	13.5(9.75-18)		

Although results from the unadjusted tests showed only a significant relationship between cannabis and other drug use, all variables were tested in the model. Only cannabis use was a significant predictor of other drug use at baseline ($\chi^2(1)= 8.5$, $p=0.004$) so no other variables were retained in the model. Confirming the results from the unadjusted analysis, in the final model (n=179), cannabis users were almost 5 times more likely to use other drugs than non-

cannabis users (exp(B)=4.79, CI 95% (1.51 – 15.18), p=0.008) (Table 5.13). Although this is an exploratory analysis, it should be mentioned that only 18 of the 179 patients whose data were included in the model were using other drugs at baseline. While this is not a violation of the assumptions for a logistic regression, such differences might not have been observed if more cannabis users had been included in the model.

Table 5.13 Logistic regression model assessing predictors of other drug use at baseline

	Odds ratio	95% CI	Sig
Univariate analysis			
Baseline total PANSS scores	1.00	1.00 – 1.03	0.833
Baseline positive PANSS scores	1.00	0.92 – 1.09	0.981
Age	1.02	0.98 – 1.07	0.383
Gender	0.34	0.09 – 1.24	0.102
Baseline BLEQ	1.21	0.91 – 1.60	0.192
Multivariate analysis (final model)			
Cannabis use at baseline	4.79	1.51 – 15.18	**0.008**

Urinary Drug Screen

Seventy-seven drug screens were performed at 3 months and 60 samples were available at 12 months. As anticipated there was better (substantial) (Landis and Koch, 1977) agreement between patients' self-reported cannabis use and urinalysis than at baseline with Cohen's kappa=0.683 and 0.692 respectively (Table 5.14). Three of the 53 self-reported non-users at 3 months and 4 of 41 at 12 months produced UDS results positive for cannabis. It is most likely that these present false negative results based on Colcateno sensitivity levels at 97%. Therefore, these patients will continue to be treated as non-users for the purposes of analysis.

Table 5.14 Level of agreement between self-reported cannabis use and urinalysis at 3 and 12 months

	Positive (%)	Negative (%)	Sig
3 months			**<0.001**
Cannabis users (n=24)	70.8	29.2	
Non-users (n=53)	5.7	94.3	
12 months			**<0.001**
Cannabis users (n=19)	78.9	21.1	
Non-users (n=41)	9.8	90.2	

Current cannabis vs non-cannabis users based on UDS results

There were no differences between current cannabis users and non-users according to UDS results rather than self report across 12-month positive and total PANSS scores (table 5.15).

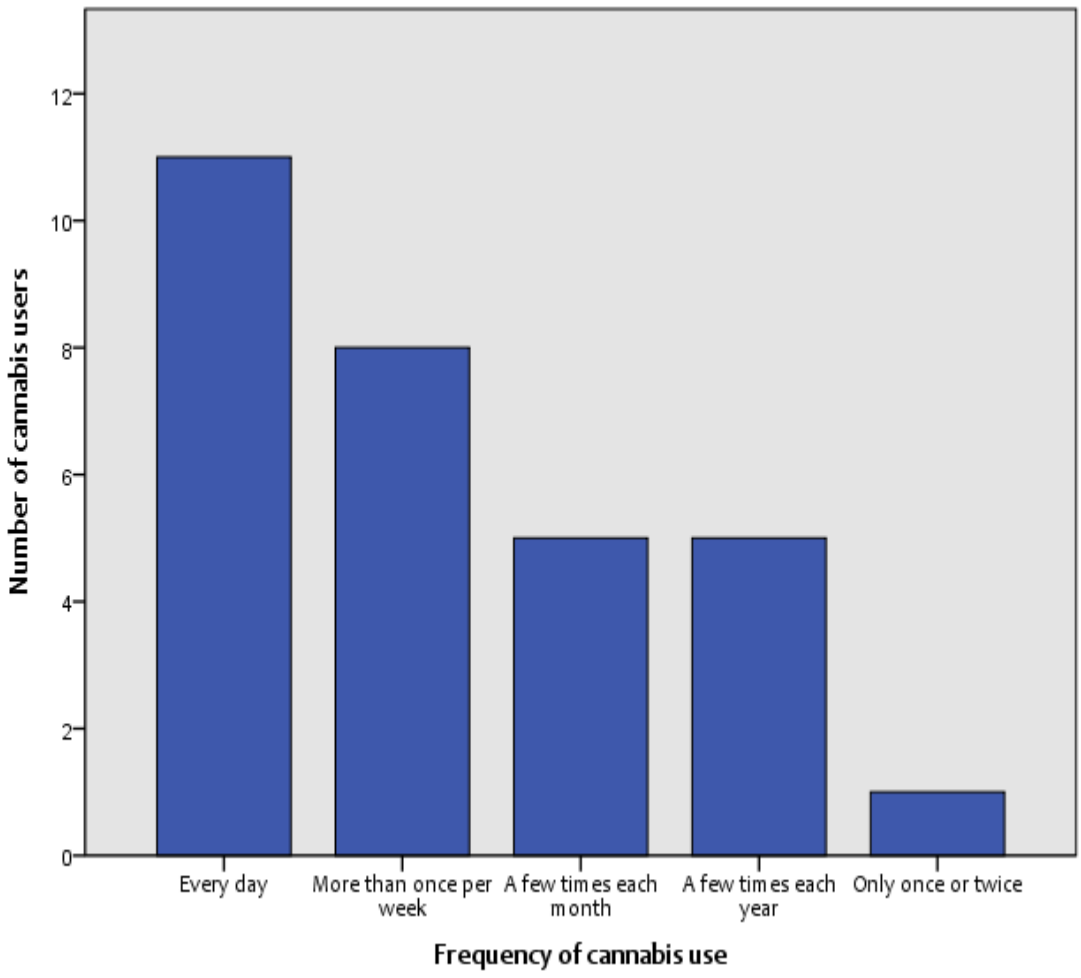
Table 5.15 Differences between current cannabis users and non-users based on UDS results

	Cannabis users	Non-users	Test	Sig.
Total PANSS scores	**(n= 18)**	**(n= 37)**	U	0.187
Median (IQR)	49 (43.5-62)	43 (35-61.5)		
Positive PANSS scores	**(n= 17)**	**(n= 39)**	U	0.100
Median (IQR)	11 (8-14.5)	9 (7-12)		

Levels of cannabis use

Data on frequency of cannabis use at 12 months were available for 30 of the 32 users. Eleven reported using cannabis every day; 8 using more than once per week; 5 using a few times each month; 5 using a few times each year and 1 having used only once or twice. Two-thirds of the cannabis users at 12 months reported using cannabis at least once per week. The available data on the levels of cannabis use at 12 months were not sufficient to test differences on PANSS scores between heavy and light users.

Figure 5.3 Frequency of cannabis use at 12 months



Missing data

Missing item data can be prorated; that is replacing the missing item score by the mean of the observed items if less than 20% of the items scores are missing as simulation studies have shown that pro-rating (or case mean substitution) is a robust method when data are missing on less than 20% of items in both random and systematic patterns (Roth et al, 1999). We, therefore, excluded 5% of the 12-month positive PANSS subscales and 12% of the 12-month total PANSS scales from analysis because more than 20% of the subscale items were missing.

5.7 Summary of findings

The main findings of this chapter were:

1. Cannabis use at 12 months was not independently associated with 12-month total PANSS scores. Baseline total PANSS scores were the only independent predictor of 12-month total PANSS scores. In the final model, where both variables were included, the association of cannabis use and 12-month total PANSS scores improved but remained non-significant.
2. Cannabis use at 12 months, baseline total PANSS scores and baseline current tobacco use were independently associated with 12-month positive PANSS scores. When all variables were tested together, only baseline total PANSS scores remained a significant predictor of 12-month positive PANSS scores.
3. Cannabis use at baseline was associated with other drug use and this remained significant after adjusting for potential confounders. Unadjusted analysis showed a significant relationship at 3 months but this was not observed at 12 months. Adjusted analysis was not possible at 3 and 12 months due to insufficient power. No other variables were significantly associated with other drug use.

5.8 Discussion

Cannabis use and symptom severity

Using a series of cross-sectional assessments this chapter described a) the association between cannabis use and total symptom severity at 12 months, b) the association between cannabis use and positive symptom severity at 12 months and c) the relationship between cannabis and other drug use at baseline, 3 months and 12 months.

Contrary to the hypothesis that patients who use cannabis at 12 months will score higher on the total PANSS scale, no significant effect of cannabis use on total PANSS scores was observed in this study. This finding is consistent with Green et al (2004) who reported a lack of association between cannabis misuse and changes in total PANSS scores between baseline and follow-up in an RCT of haloperidol vs olanzapine among patients with psychosis. In contrast, a number of other studies have found cannabis use to be associated with total symptom severity (Martinez-Arevalo et al, 1994; Degenhardt et al, 2007; Linszen et al, 1994; Hinton et al, 2007).

Although cannabis use independently predicted 12-month positive PANSS scores, this relationship did not remain significant when adjusting for potential confounders. This is consistent with the findings by Stirling et al (2005) who observed a similar pattern of positive symptomatic outcome between cannabis users and non-users in a study of psychosis and neurocognition but inconsistent with the results of five studies (Hinton et al, 2007; Wade et al, 2006; Hides et al, 2006; Addington and Addington 2007; Grech et al, 2005), which found cannabis use to significantly affect positive symptoms even after controlling for potential confounders.

Although no consensus has been reached on the relationship between cannabis use and psychotic outcomes, this study observed results that do not confirm the hypotheses. A number of issues might help explain these findings, which although not altogether surprising are not strongly supported by previous research. Cannabis users at baseline rated higher in total and positive PANSS scores than non-users and were more likely to be younger, male and report lifetime and current use of tobacco, alcohol and other drugs; factors that could have affected follow-up psychopathology. The strength of the association

between cannabis use and total PANSS scores could have been further underestimated by the higher non-completion rates of 12-month total PANSS scores by patients with more severe baseline symptomatology (total and positive PANSS scores). Baseline symptom severity across the sample was low which could have also masked a significant relationship if patients with more mental health problems were lost to follow-up. Cannabis users were not less likely than non-users to complete 12-month symptom severity assessments and so the association would not have been biased by the lack of a sufficient number of cannabis users. Although these observations could have accounted for the loss of a significant effect by cannabis use on positive symptoms in the multivariate analysis, this finding seems to be consistent with suggestions from previous studies that adjusting for psychotic symptoms at some earlier point will substantially reduce the size of the relationship between cannabis use and psychotic symptoms at follow-up (Arseneault et al, 2002). The lack of a significant relationship between cannabis use and positive symptoms at 12 months, when adjusting for potential confounders, could have also been affected by the higher rate of male patients that failed to complete the assessment. As cannabis users tended to be male, it is possible that the lower completion rate of positive PANSS subscale by men could have underpowered the adjusted regression.

It is important to address the finding that baseline tobacco use was associated with more positive symptoms at 12 months. This observation has not been previously reported most likely because adequate adjustment for potential substance use confounders has not been systematically adopted. Prevalence of tobacco use in patients with schizophrenia has been reported around 85%, much higher than in the general population (~30%) (De Leon, 1996). Kelly and McCreadie (2000) found that 68% of patients with schizophrenia were also heavy smokers (25 cigarettes or more per day) compared to only 11% of the general population who smoke (Olincy et al, 1997).

The fact that tobacco use might be an indication for poorer outcome in schizophrenia is one theory that has received most attention among a number of suggestions that aim to explain the high rates of smoking in this population. Smokers are often younger and male and score higher on positive symptom

scales (Ziedonis et al, 1994). This commonly describes the characteristics of the present sample and observing an independent effect of tobacco use on psychotic outcomes is justified. Even so, the strongest predictor of 12-month positive psychotic symptoms was still baseline total symptom severity as the significant relationship between tobacco use and psychotic outcomes was lost when adjustment for confounders was made.

Strengths and limitations

The main strength of this study is that it investigated and consistently controlled for potential confounders identified from baseline comparisons between cannabis users and non-users. These adjustments included measures of baseline psychopathology and substance use, which can independently affect psychotic outcomes. Even studies that reported similar results (Green et al, 2004; Stirling et al, 2005) did not adequately control for potential confounders and this is widely lacking in research that supported a relationship between cannabis use and psychotic outcomes. An additional advantage to this rigorous method was the use of a univariate regression model, which allowed the separate investigation of potential confounders and only retained those with significant effects. A traditional method of simultaneously entering variables into the model is not likely to have produced different results but would not have allowed for an assessment of individual associations to be examined.

A further advantage of this study is the strict criteria for definition of first-episode psychosis and cannabis use at baseline and the inclusion of patients from all psychosis groups. First episode was identified as first contact, rather than admission, with services so that recruitment included both inpatients and outpatients but only those who had experienced their first episode in the preceding six months were included in the study. This way cannabis reduction or cessation due to continuous contact with services as well as improvement in mental health state from treatment involvement was prevented. Cannabis use at baseline was defined as any use within the preceding 12 months to ensure that occasional users and patients who had stopped using just before presentation or admission were not improperly classified as non-users. This criterion was not applied to the 3- and 12-month follow-up to allow for a clear distinction between

persistent and non-persistent users. Patients with any diagnosis of a psychotic disorder were included in the analyses. Zammit et al (2008) have highlighted a trend whereby effects of cannabis use on symptom severity are observed in mainly schizophrenic populations but such an association is not always present when all psychotic diagnoses are included. Although this might be worthy of further investigation, it is unlikely that it caused the lack of association in this study as previous research that reported significant results had included all psychotic diagnoses (Grech et al, 2005). Patients with a diagnosis of substance-induced psychosis were included in the study and it might be possible that the effects of cannabis are different between those with and those without such diagnosis although Hides et al (2006) found that their results did not change when the substance-induced psychotic patients were excluded from the analysis.

A further strength of this study is the use of urinalysis to validate self-reported cannabis use and is only the second study to employ drug screens at all assessment points (van Dijk et al, 2012). Although agreement was not as high as found in the only previous study that investigated reliability statistically (Cohen's kappa=0.90; Hides et al, 2006), it was still satisfactory and as anticipated higher in the 3- and 12-month follow-ups than at baseline. About a third of users still produced negative samples at 3 and 12 months, which is likely to have contributed to an underestimation of the level of agreement.

The sample size of this study is at the lower end of a very wide range of sample sizes in previous research (56 to 262) but even so it is not likely to have affected the results. Although a large sample size would ensure adequate power to detect significant associations, some studies with small sample sizes have reported positive findings (Martinez-Arevalo et al, 1994; Stirling et al, 2005; Hides et al, 2006). However, the relatively small sample size prevented any further classification of cannabis exposure based on frequency, quantity or duration before presentation. Some research that has reported significant results (Addington and Addington, 2007) as well as those studies that did not observe associations (Stirling et al, 2005) also failed to examine cannabis exposure in more detail.

The study design whereby data were collected in a cross-sectional manner did not allow for cannabis use information between the follow-up points to be

utilised. Absence of a significant association between cannabis use and symptom severity might be attributed to changes in levels of substance use immediately after baseline and between follow-ups. If patients reduced their cannabis use following contact with services, they would still be classified as users at the various follow-ups although their mental health would have invariably improved. For the same reason it was not feasible to investigate changes in cannabis use in such way as to identify persistent users and non-users as well as baseline users who stopped and baseline non-users who initiated use at some future point. It would need vigorous longitudinal assessments to ascertain continuity, discontinuity and initiation of cannabis use although time-group interactions were not observed in the study by Hinton et al (2007), indicating that patterns of change did not differ between cannabis groups. Measuring compliance to medication is similarly challenging but unlikely to have influenced the results. Although it is unclear how adherent patients are with treatment in between follow-ups, the high rates of medication compliance are consistent with the low symptomatology.

Two thirds of the sample was male and male patients were also more likely to be cannabis users. Gender differences have been shown to exist in the course of schizophrenia (Morgan et al, 2008) but have presented women as having a less continuous course of illness and better functioning. This is unlikely to have influenced the results of this study, as findings already show a low symptomatology even with the high male to female ratio. Similar to these findings, van Diijk et al (2012) included a number of reliable measures and a wide range of possible confounders but still observed a lack of association between cannabis use and psychotic outcomes in a first-episode, male-only psychotic population.

Finally, this study did not investigate the relationship between cannabis use and negative symptoms. Paucity of research reporting significant effects of cannabis use on negative symptoms and the fact that none of the studies included in the systematic review observed such a relationship suggest that cannabis research should focus on clarifying the possible of effects of use on total and positive symptom severity. In addition, no significant differences on

negative symptoms were found from comparisons between cannabis users and non-users at baseline.

Cannabis and other drug use at baseline, 3 months and 12 months

In keeping with the results from the unadjusted analysis, cannabis use was the only predictor of other drug use at baseline when controlling for potential confounders. A similar pattern of unadjusted association was observed at 3 months although numbers were not sufficient to test this finding in a regression model. Unadjusted analysis at 12 months did not show a significant effect of cannabis use on other drug use and a regression model was not utilised due to the lack of sufficient numbers.

Insufficient power is most likely to have led to the lack of association between cannabis and other drug use at 12 months. The low rates of current, illicit drug use at baseline (20%, see Chapter 4; section 4.5) are consistent with the findings from previous research reporting on illicit drug use in psychotic populations (Lammertink et al, 2001) but this rate further decreased at subsequent follow-ups due to drop-out. The number of patients who used cannabis and any of the other illicit substances at baseline and 3 months is similar (77.8%) but decreases by almost a third at 12 months (57.1%). Even if numbers were sufficient, a lack of association at 12 months could have still been observed since a significant naturalistic reduction of substance use occurs over time in psychotic populations (Addington and Addington , 2007). This might already partly explain the differences in association between cannabis and other drug use over the follow-up period although the lack of power makes any interpretation difficult.

The rates of concurrent cannabis and other illicit substance use at baseline are consistent with those reported by Hinton et al (2007). Most research tends to report rates of poly-substance use, including alcohol, when considering the characteristics of cannabis users so whether these findings are widely representative is uncertain. The association of cannabis and other drug use while controlling for potential confounders was assessed and this, to our knowledge, is the first investigation of its kind in patients with psychosis. A strong trend emerged from unadjusted and adjusted analyses with cannabis use being the

only predictor of concurrent illicit drug use. No other variables were independently associated with illicit drug use.

Due to the lack of psychosis research reporting on such an association, present results can only be discussed in comparison to general population studies, which have mainly focused on the extent to which cannabis acts as a 'gateway drug' that leads to the use of other illicit substances. The gateway theory (Kandel, 2003) proposes a causal, sequential association where cannabis use (a) precedes other illicit substance use and (b) increases the likelihood of future illicit substance use. The present findings are not suitable to provide evidence in favour or against this theory, as only concurrent use was examined and, where this was established, temporal sequence of cannabis and other drug use was not ascertained. Results are similar to reports by Fergusson et al (2006) who found, during a 25-year study, that increasing cannabis use in any year was associated with increasing rates of other illicit substance use as well as findings from a 12-year study which showed that regular cannabis use predicted the maintenance of other illicit drug use (Swift et al, 2012). These similarities should be interpreted with caution as both studies strictly defined cannabis exposure and concentrated on the effects of varying frequencies of use, a distinction that was not applied in the current study.

Any meaningful inferences directly from the present results or through comparisons with general population studies are bound to be problematic at least due to the relatively small sample size and differences in sample characteristics, definition of cannabis exposure and measurement of outcomes. Persistent cannabis use in the general population has been associated with psychosocial harm (Macleod et al, 2004) and in patients with psychosis it has demonstrated some poorer prognostic outcomes (Zammit et al, 2008) but the association between persistent concurrent cannabis and other illicit substance use in the general or psychiatric populations has not been examined. What our findings suggest is that there is a strong, albeit unconfirmed, association between current cannabis and other illicit drug use in a psychotic population at study entry, which warrants further investigation to examine research or clinical implications.

5.9 Summary

This chapter described the findings from a series of cross-sectional assessments investigating the effects of cannabis use on total and positive symptom severity at 12 months and its association with other drug use at 3 time points. Cannabis use was not associated with either total or positive PANSS scores at 12 months. Baseline cannabis use was associated with other drug use but this finding could not be replicated at 3 and 12 months due to insufficient numbers. In the next chapter, the reasons for cannabis use at baseline, 3 months and 12 months are examined.

Chapter 6 – Reasons for cannabis use at baseline, 3 months and 12 months

6.1 Synopsis

Despite some inconsistent findings for the reasons for cannabis use in patients with psychosis (Chapter 2; section 2.3), the evidence to date points towards an 'alleviation of dysphoria' model. The self-medication hypothesis (Khantzian, 1985) has received little support over the years with research showing that patients with psychosis use cannabis mostly because of its enhancing effects, to 'get high' or reduce unpleasant states such as depression or boredom. There has been no research so far examining the changes in reasons for cannabis use over time. In this chapter, reasons for cannabis use in first-episode psychosis will be assessed and compared at 3 time points.

It was observed, at all 3 time points, that enhancement was much more important to patients than any other reason for cannabis use. A post-hoc analysis also showed that patients had stronger reasons for their cannabis use at baseline than at 12 months. These findings support the emergent 'alleviation of dysphoria' model and show that reasons for use may change over time and be amenable targets for intervention.

6.2 Hypotheses

1. At each time point, patients who use cannabis will be more likely to do so because of its enhancing effects and for social reasons rather than to 'self-medicate'.
2. As the literature in the field of changes in reasons for cannabis use over time is absent, it was decided not to form a hypothesis, as there was no evidence base for justification. Rather, the changes in reasons for cannabis use across the 3 time points will be examined in a post-hoc analysis.

6.3 Sample selection

At baseline, 219 patients were assessed but information on cannabis use was available for 198 patients (84 users and 114 non-users). At 3 months, data on cannabis use were available for 108 of the 109 patients who were assessed (29 users and 79 non-users) and at 12 months, 108 patients were assessed but information on cannabis use was available for 101 patients (32 users and 69 non-users). Sixty-six of the 84 cannabis users completed the Reasons for Use Scale (RFUS) at baseline, all 29 at 3 months and all 32 at 12 months (Table 6.1).

Table 6.1 Number of participants with data on cannabis use and RFUS at baseline, 3 months and 12 months

	Cannabis users/ Completers	Non-users
Baseline	84/66	114
3 months	29/29	79
12 months	32/32	69

6.4 Measures

The Reasons for Use Scale (RFUS)

The Reasons for Use Scale (Spencer et al, 2002) was used to assess reasons for cannabis use. This is a 26-item self-report instrument that includes items from the Drinking Motives Questionnaire (DMQ; Cooper, 1994) and additional motives specific to symptoms of mental illness. Internal reliability of the scale has been demonstrated in patients with psychotic disorders (Spencer et al., 2002). It is administered to better understand participants' reasons for substance use and thus tailor any intervention to meet an individual's needs. The 26 items relate to the 5 subscales that are believed to reflect a participant's reasons for drug use (Table 6.2):

1. Enhancement
2. Social motive
3. Coping with unpleasant affect
4. Conformity and acceptance
5. Relief of positive symptoms and side effects

Table 6.2 Subscales and subscale items of the RFUS

Subscales	Subscale items
Enhancement	- Because it makes you feel good - Because it's fun - To get high
Social motive	- Because it's what most of your friends do when you get together - Because it makes a social gathering more enjoyable - As a way to celebrate - To be sociable
Coping with unpleasant affect	- Because it helps when you are feeling nervous - Because it helps when you are feeling depressed - To forget your worries - To feel more motivated - To make it easier to sleep - To help me concentrate - Because you feel more self-confident or sure of yourself - To relieve boredom - To decrease restlessness - To slow down racing thoughts - To relax
Conformity and acceptance	- So you won't feel left out - To be liked - To help you talk to others - To be part of a group - Because your friends pressure you to do it
Relief of positive symptoms and side effects	- To get away from the voices - To reduce side effects of medication - To feel less suspicious/paranoid

Participants complete the questionnaire about one substance only and in this case, cannabis. The questionnaire utilises a 5-point scale that reflects how often they use the substance for each specific reason: never/almost never (0), some of the time (1), half of the time (2), often (3), and almost always/always (4). The scale is rated by the mean score on each subscale.

6.5 Analyses

Participants rated 5 reasons for their cannabis use at the 3 time points and the analysis examined the differences between reasons for use at each time point and the differences in these ratings between baseline, 3 months and 12 months.

A series of paired-sample t-tests were carried out to test differences between mean scores on each subscale of the RFUS at baseline, 3 months and 12 months. Ten pairs were created from the 5 subscales: enhancement, social motive, coping with unpleasant affect, conformity and acceptance and relief of positive symptoms and side effects. The Bonferroni correction at 0.05 was used to correct for multiple testing of the paired-sample t-tests.

In order to assess differences in mean scores on the RFU subscales as well as test whether these differences change over time, a random intercept model was used. Fixed effects of reason (5 subscales) and time (baseline, 3 months and 12 months) were included in the model, in addition to a random effect of participant. This model allows subjects who had data at any of the time points to contribute to the analysis - unlike a repeated-measures ANOVA test, which excludes subjects with any missing values.

6.6 Results

Ten paired sample t-tests were performed for baseline, 3 months and 12 months to assess any differences between mean scores on the RFU subscales. Results are presented in Table 6.3, 6.4 and 6.5, respectively.

Table 6.3 Differences in reasons for cannabis use at baseline

Pairs	Reasons	M	SE	t(df)	Sig
1	Enhancement	3.2	0.14	6.26(65)	**<0.001**
	Social motive	2.3	0.13		
2	Enhancement	3.2	0.14	6.36(64)	**<0.001**
	Coping with unpleasant affect	2.3	0.11		
3	Enhancement	3.2	0.14	11.04(64)	**<0.001**
	Conformity and acceptance	1.5	0.10		
4	Enhancement	3.2	0.14	10.51(64)	**<0.001**
	Relief of positive symptoms and side effects	1.4	0.10		
5	Social motive	2.3	0.13	-0.15(64)	ns
	Coping with unpleasant affect	2.3	0.11		
6	Social motive	2.3	0.13	7.50(64)	**<0.001**
	Conformity and acceptance	1.5	0.10		
7	Social motive	2.3	0.13	5.49(64)	**<0.001**
	Relief of positive symptoms and side effects	1.4	0.10		
8	Coping with unpleasant affect	2.3	0.11	7.15(64)	**<0.001**
	Conformity and acceptance	1.5	0.10		
9	Coping with unpleasant affect	2.3	0.11	8.62(64)	**<0.001**
	Relief of positive symptoms and side effects	1.4	0.10		
10	Conformity and acceptance	1.5	0.10	0.91(64)	ns
	Relief of positive symptoms and side effects	1.4	0.10		

Table 6.4 Differences in reasons for cannabis use at 3 months

Pairs	Reasons	M	SE	t(df)	Sig
1	Enhancement	3.1	0.26	4.6(28)	**<0.001**
	Social motive	2.0	0.18		
2	Enhancement	3.1	0.26	2.63(28)	**0.014**
	Coping with unpleasant affect	2.4	0.16		
3	Enhancement	3.1	0.26	7.03(28)	**<0.001**
	Conformity and acceptance	1.3	0.08		
4	Enhancement	3.1	0.26	5.11(28)	**<0.001**
	Relief of positive symptoms and side effects	1.6	0.15		
5	Social motive	2.0	0.18	-2.03(28)	ns
	Coping with unpleasant affect	2.4	0.16		
6	Social motive	2.0	0.18	4.90(28)	**<0.001**
	Conformity and acceptance	1.3	0.08		
7	Social motive	2.0	0.18	1.78(28)	ns
	Relief of positive symptoms and side effects	1.6	0.15		
8	Coping with unpleasant affect	2.4	0.16	7.50(28)	**<0.001**
	Conformity and acceptance	1.3	0.08		
9	Coping with unpleasant affect	2.4	0.16	6.60(28)	**<0.001**
	Relief of positive symptoms and side effects	1.6	0.15		
10	Conformity and acceptance	1.3	0.08	-1.79(28)	ns
	Relief of positive symptoms and side effects	1.6	0.15		

Table 6.5 Differences in reasons for cannabis use at 12 months

Pairs	Reasons	M	SE	t(df)	Sig
1	Enhancement	3.3	0.19	6.75(31)	**<0.001**
	Social motive	1.8	0.14		
2	Enhancement	3.3	0.19	5.54(31)	**<0.001**
	Coping with unpleasant affect	2.1	0.11		
3	Enhancement	3.3	0.19	10.84(31)	**<0.001**
	Conformity and acceptance	1.2	0.05		
4	Enhancement	3.3	0.19	7.83(31)	**<0.001**
	Relief of positive symptoms and side effects	1.4	0.12		
5	Social motive	1.8	0.14	-1.82(31)	ns
	Coping with unpleasant affect	2.1	0.11		
6	Social motive	1.8	0.14	4.91(31)	**<0.001**
	Conformity and acceptance	1.2	0.05		
7	Social motive	1.8	0.14	2.50(31)	**0.018**
	Relief of positive symptoms and side effects	1.4	0.12		
8	Coping with unpleasant affect	2.1	0.11	8.32(31)	**<0.001**
	Conformity and acceptance	1.2	0.05		
9	Coping with unpleasant affect	2.1	0.11	5.34(31)	**<0.001**
	Relief of positive symptoms and side effects	1.4	0.12		
10	Conformity and acceptance	1.2	0.05	-1.59(31)	ns
	Relief of positive symptoms and side effects				

Baseline

Enhancement was rated by participants as much more important than social use ($t(64)=6.26$, $p<0.001$), coping with unpleasant affect ($t(64)=6.36$, $p<0.001$), conformity and acceptance ($t(64)=11.04$, $p<0.001$) and relief of positive symptoms and side effects ($t(64)=10.51$, $p<0.001$).

Social motive was given higher value by cannabis users than conformity and acceptance ($t(64)=7.50$, $p<0.001$) and relief of positive symptoms and side effects ($t(64)= 5.49$, $p<0.001$) but not coping with unpleasant affect.

Coping with unpleasant affect was given a higher rating than conformity and acceptance ($t(64)=7.15$,$p<0.001$) and relief of positive symptoms and side effects ($t(64)=8.62$, $p<0.001$).

3 months

Enhancement was again rated as more important than social use ($t(28)=4.6$, $p<0.001$), coping with unpleasant affect ($t(28)=2.63$, $p=0.014$), conformity and acceptance ($t(28)=7.03$, $p<0.001$) and relief of positive symptoms and side effects ($t(28)=5.11$, $p<0.001$).

Social motive was more important to cannabis users than conformity/acceptance ($t(28)= 4.90$, $p<0.001$) but not rated higher than relief of positive symptoms and side effects or coping with unpleasant affect.

Coping with unpleasant affect was rated as more important than conformity and acceptance ($t(28)=7.50$,$p<0.001$) and relief of positive symptoms and side effects ($t(28)=6.60$, $p<0.001$).

12 months

Enhancement was still rated as more important than social use ($t(31)=6.75$, $p<0.001$), coping with unpleasant affect ($t(31)=5.54$, $p<0.001$), conformity and acceptance ($t(31)=10.84$, $p<0.001$) and relief of positive symptoms and side effects ($t(31)=7.83$, $p<0.001$).

Social motive was more important to cannabis users than conformity and acceptance ($t(31)= 4.91$, $p<0.001$) and relief of positive symptoms and side effects ($t(31)= 2.50$, $p=0.018$) but not rated higher than coping with unpleasant affect.

Coping with unpleasant affect was rated as more important than conformity and acceptance ($t(31)=8.32, p<0.001$) and relief of positive symptoms and side effects ($t(31)=5.34$, $p<0.001$).

Conformity and acceptance was not rated as more important than relief of positive symptoms and side effects at baseline, 3 months or 12months.

In summary, at each time-point patients rated enhancement as much more important for their cannabis use than any other reason.

Social motive was more important than conformity and acceptance and relief of positive symptoms and side effects but patients appeared to give it equal weight when compared to coping with unpleasant affect at baseline, 3 and 12 months. At 3 months patients didn't rate social motive as more important than relief of positive symptoms and side effects.

Coping with unpleasant affect was found to be much more important to patients than conformity and acceptance and relief of positive symptoms and side effects at all 3 time points.

Conformity and acceptance failed to rate higher than relief of positive symptoms and side effects at baseline, 3 months or 12 months (Table 6.3).

The Bonferroni correction at 0.05 (0.05/30= 0.0017) showed that 21 out of 23 t-tests remained significant. Enhancement/coping with unpleasant affect at 3 months and social motive/relief of positive symptoms and side effects at 12 months lost their significance at 0.05. The large number of significant results that were consistent across baseline, 3 and 12 months makes it unlikely that findings reflect false positive observations and differences cannot be attributed to random chance alone.

Table 6.6 Comparisons between mean RFU subscale scores at each time point

	Baseline	3 months	12 months
Subscales			
Enhancement (E)	SM / C- / CA / R+	SM / C- / CA / R+	SM / C- / CA / R+
Social motive (SM)	CA / R+ / C-[2]	CA / R+[2] / C-[2]	CA / R+[1] / C-[2]
Coping with unpleasant affect (C-)	CA / R+	CA / R+	CA / R+
Conformity and acceptance (CA)	R+[2]	R+[2]	R+[2]
Relief of positive symptoms and side effects (R+)	-	-	-

All significance levels at p<0.001 besides
[1] p<0.05
[2] non-significant
- comparison already performed in previous cells

A random intercept model analysis was performed to explore differences between mean scores on the RFU subscales while controlling for time with 'relief of positive symptoms and side effects' and 'baseline' entered as the constant variables. Both time ($F(2,567)=108.1$, $p<0.001$) and reason ($F(4, 532)=4.5$, $p<0.001$) were found to significantly contribute to the model. Enhancement reasons for cannabis use ($M=3.01$) were more important than relief of positive symptoms and side effects ($M=1.26$; $t=17.48$, $p<0.001$). Social motive was chosen as more significant in sustaining cannabis use ($M= 1.93$) than relief of positive symptoms and side effects ($M=1.26$; $t=6.65$, $p<0.001$). Similarly, coping with unpleasant affect was rated higher as a reason for cannabis use ($M=2.1$) than relief of positive symptoms and side effects ($M=1.26$), ($t=8.35$, $p<0.001$). Patients did not rate conformity and acceptance as a significantly more important reason for cannabis use than relief of positive symptoms and side effects (Table 6.4, Figure 6.1). These results confirm earlier baseline observations from the paired-sample t-tests.

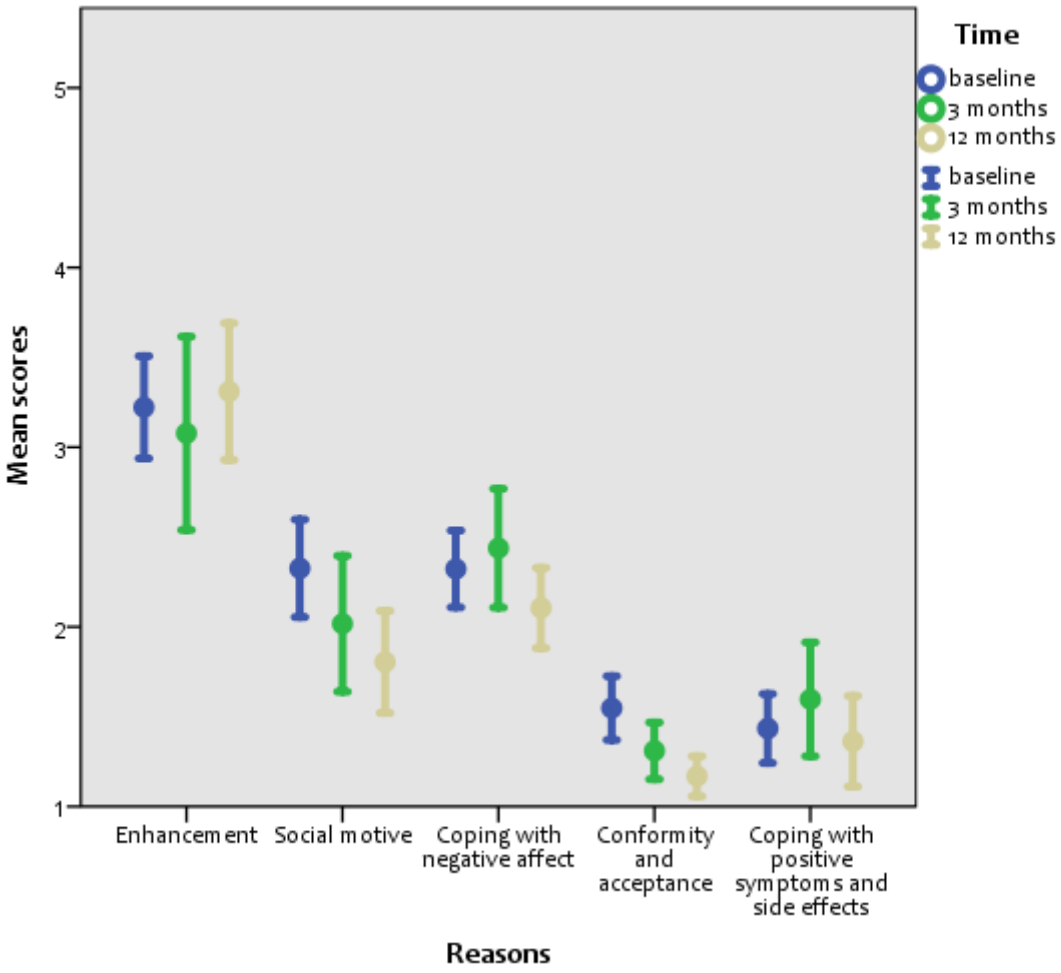
Time appeared to have a significant effect on scores when controlling for reason. On average, scores on any subscale were .28 points higher at baseline than 12 months ($t=2.97$, $p<0.05$) but no significant differences were observed in mean subscale scores between 3 months and 12 months. This means that patients felt more strongly about each reason sustaining their cannabis use at baseline than they did at 12 months but did not rate reasons for use at 3 months higher than at 12 months (Table 6.4, Figure 6.1).

The distribution of the residuals was examined graphically following this analysis and no violations of the assumptions of the random intercept model were found.

Table 6.7 Random intercept model testing the differences in reasons for cannabis use while controlling for time

	t	95% CI	Sig
Reason			
Relief of positive symptoms and side effects			
Enhancement	17.48	1.56 – 1.95	**<0.001**
Social motive	6.65	0.47 – 0.86	**<0.001**
Coping with unpleasant affect	8.35	0.64 – 1.04	**<0.001**
Conformity and acceptance	-0.56	-0.25 - 0.14	0.572
Time			
12 months			
Baseline	2.97	0.09 - 0.47	**0.003**
3 months	1.4	-0.06 - 0.36	0.161

Figure 6.1 Box-plot of changes in reasons for cannabis use at the 3 time-points



6.7 Summary of findings

The main findings of this chapter were:

1. Enhancement followed by social motive was the most important motivator for cannabis use at all 3 time-points.
2. Reasons for cannabis use endorsed by patients with psychosis do not provide support for the traditional self-medication hypothesis.
3. Patients felt much more strongly about their reasons for use at baseline than 12 months but this difference was not observed between 3 and 12 months.

6.8 Discussion

Using a series of cross-sectional assessments this chapter described the reasons for cannabis use among patients with psychosis at baseline, 3 months and 12 months. In a post-hoc analysis changes in the reasons endorsed between the 3 time points were examined.

Consistent with the hypothesis that enhancing and social effects would be more important reasons for use than attempts to self-medicate, as in the general population (Cooper, 1994), patients who used cannabis at each time point were more likely to do so because of its enhancing effects rather than any other motive. Social use followed closely but was not rated higher than coping with unpleasant affect at any follow-up point and was as important as relief of positive symptoms and side effects at 3 months. These data support previous studies that investigated reasons for cannabis use in patients with psychosis as no evidence for the self-medication hypothesis was observed (Schaub et al, 2008; Addington and Duchak, 1997; Green et al, 2004; Schofield et al 2006; Goswami et al, 2004; Fowler et al, 1998). However, only two studies (Goswami et al, 2004; Green et al, 2004) found that enhancing effects were the most important reason for cannabis use among patients with psychosis. The rest of the studies reported that coping with unpleasant affect- mainly relief of boredom and anxiety- were rated much higher than any other reason followed by enhancement and social use. This is similar to findings reported by Henquet et al (2010) who found that patients were more sensitive to the mood-enhancing effects of cannabis (i.e. large and significant decreases in negative affect were observed after cannabis use).

The diversity of instruments used to assess reasons for use might explain this slight variability. Misclassification of the social motives is likely to have occurred as most of the previous studies utilized lists, which only included one or two reasons related to social motive (Addington and Duchak, 1997). These appear to resemble the items on the conformity and acceptance rather than the social motive subscale of the present instrument, which distinguishes between social enhancement reasons and reasons related to social pressure. This has possibly led to underestimation of the significance of social motives for cannabis use in previous research. On the contrary, the two studies that found

enhancement followed by social motives to be the most important motivators for cannabis use had clearly described social motives as 'social activity' and 'to increase socialization' (Goswami et al, 2004; Green et al, 2004).

A post-hoc analysis showed that patients felt much more strongly about their reasons for use at baseline than at 12 months although no difference was observed between 3 and 12 months. It is likely that contact with services and treatment for psychosis incorporates some intervention targeting cannabis use. Over time patients might have had the opportunity to explore the reasons for their cannabis use and possible effects it has on their illness trajectory, which may have reduced the level of certainty they feel over what sustains their use. It has also been previously suggested that the reasons patients endorse for their cannabis use do not always appear to be justified by the subsequent perceived effects of the actual use. For instance, patients reported using cannabis to relieve anxiety or depression or to relax but appeared not to gain relief from these symptoms or achieve relaxation after use (Addington and Duchak, 1997; Green et al; 2004). Similarly with encouraging patients to explore their reasons, supporting them in recognizing the perceived and actual effects of cannabis use and emphasizing any discrepancies is likely to have lessened the confidence in the reasons they had considered to be previously sustaining their use. It is also possible that the lower rate of completion of the RFUS at 3 and 12 months might have overestimated how strongly patients feel about their reasons at baseline and/or underestimated this effect at 3 and 12 months. The lack of significant differences between 3 and 12 months, where similarly low completion rates were achieved, further supports this likelihood.

Strengths and limitations

The main strength of this study is that it utilised a validated and reliable measure for assessing reasons for cannabis use in patients with psychosis. This is a comprehensive instrument, which comprises a Likert scale to measure how much of the time each reason has played an important role in using cannabis. Research so far has been mostly conducted using lists of proposed reasons that patients complete based on a YES/NO response (Schaub et al, 2008). Patients with schizophrenia have been known to appear more suggestible (Kot and

Serper, 2002) so the use of a Likert scale rather than an invitation to simply accept or reject an already proposed reason is more likely to prevent frequent positive responses while increasing variability and strengthening the significant differences observed between reasons.

Another advantage of this study is the sample size at baseline, which is the largest among studies that have investigated reasons for cannabis use in psychosis. The lower sample sizes at 3 and 12 months are still relatively large compared to previous research (Goswami et al, 2004). The consistency between findings from this study and previous research with smaller groups suggests that results are unlikely to be due chance and are further validated by the benefit of a larger sample.

A further strength of this study was the inclusion of both inpatients and outpatients. Research so far has only investigated reasons for cannabis use in stable, outpatient populations. This has occasionally been intentional to avoid bias from severely ill patients who might have already failed in self-medication attempts and would be less likely to choose this reason for their cannabis use (Goswami et al, 2004). The inclusion of hospitalised and community patients' reasons for use validates previous research so excluding inpatient groups is not likely to have affected the results. The low psychopathology rates in this sample also indicate a relative remission and further avoid potential bias from severely ill patients. However, it might be argued that low symptom severity might prevent patients from choosing self-medication reasons as the stability of their illness might allow them to enjoy cannabis for other reasons, which they are more likely to endorse as important. It is not possible to assess this likelihood as no research has investigated reasons for cannabis use in patients with varying degrees of symptom severity.

The inclusion of patients with psychosis has been another advantage of this study. Most previous research has examined reasons for cannabis use in patients with schizophrenia and only two had included patients with wider psychotic disorders (Green et al, 2004; Schofield et al, 2006). Present findings contribute to the evidence base by showing that reasons for cannabis use remain fairly stable in psychotic populations and are consistent with results from research in schizophrenia-only patients.

This study did not take into account the different classes of medication by which patients were treated. Typical antipsychotics have been shown to have particularly unfavourable effects for patients with schizophrenia who use cannabis (Marchese et al, 2003). Atypical neuroleptics are related to a different group of side effects, such as weight gain and other metabolic irregulations (Rummel-Kluge et al, 2010). The only study that considered this difference found that fewer patients treated with atypical rather than typical antipsychotics were likely to report that cannabis improved the feeling of being 'slowed down' caused by the medication (Addington and Duchak, 1997). However, Schaub et al (2008) showed that patients treated with atypical antipsychotics chose only one reason more often than healthy controls and that was using cannabis to 'reduce boredom'. There is a possibility that different classes of antipsychotics as well as treatment with antidepressant or anxiolytic medication or a combination of both might lead to over- or understating the importance that certain reasons have in sustaining cannabis use. This would also obscure findings when investigating reasons for cannabis use in treated and medication-free patients, although no research has examined this distinction so far.

Although the sample size was adequately large for this investigation, the number of patients completing the RFUS was not sufficient to allow for further analysis based on classification of cannabis exposure in terms of frequency or quantity. Cannabis abusers have been shown to endorse illness and medication-related reasons for use more often than cannabis users (Fowler et al, 1998). Similarly, in the study by Schofield et al (2006) greater amount and frequency of cannabis use was observed when side effects were motivators. On the contrary, daily cannabis users were more likely to state they used cannabis to increase pleasure and go along with the group (Schaub et al, 2008). None of the studies observed an increased report of self-medication reasons for use across the different cannabis groups. Lack of endorsement of self-medication motivators in this study might have been due to infrequent cannabis use. This was not possible to consider although studies that examined different patterns of use have not consistently reported a greater incentive to relief positive symptoms or medication side effects by patients using cannabis at higher frequency or greater amounts.

6.9 Summary

This chapter described the results from a cross-sectional design used to assess the reasons for cannabis use in patients with psychosis at 3 time points and reported the findings from a post-hoc analysis on the changes in these reasons between baseline, 3 months and 12 months. Enhancement was the most commonly endorsed reason for use across the 3 times points followed by social motives. The post-hoc analysis demonstrated that patients' ratings for any reason at baseline were significantly higher than at 12 months. In the next chapter readiness to change cannabis use at baseline and 3 months is examined as a measure of cannabis use outcome at 12 months.

Chapter 7 – Readiness to change as a predictor of cannabis use outcome

7.1 Synopsis

Motivation to change drug use has been extensively researched in primary substance users but it is just emerging as an area of interest in populations with co-morbid psychiatric and substance use disorders (Chapter 1; section 1.5.2). The limited literature on readiness to change drug use in psychiatric populations has presented mixed findings. Although higher readiness to change has been associated with lower rates of drug use, lower readiness to change has shown better treatment involvement and adherence (Chapter 2; section 2.4). No research so far has examined readiness to change as a measure of cannabis use outcome in patients with psychosis and RTC instruments have not been validated for use in psychotic populations. As many cannabis users with psychosis drop out of treatment due to lack of motivation, readiness to change is an important aspect of clinical intervention as it is a malleable construct that might affect prognosis. In this chapter, readiness to change cannabis use at baseline and 3 months will be examined as a measure of cannabis use outcome at 12 months using the Readiness Ruler and the Readiness to Change Questionnaire-Treatment Version.

Assessment of readiness to change as a predictor of cannabis use and comparison of the utility of the questionnaires to address this was not statistically possible, due to the low number of cannabis users who completed the instruments, and results are summarized descriptively.

7.2 Hypotheses

1. Readiness to change at baseline according to the Readiness Ruler will be associated with cannabis non-use at 12 months.
2. Readiness to change at 3 months according to the Readiness Ruler rather than the Readiness to Change Questionnaire- Treatment Version will be associated with cannabis non-use at 12 months.

7.3 Sample selection

Two hundred and nineteen patients were assessed at baseline, 108 at 3 months and 109 at 12 months (Chapter 5; section 5.4). Of these, information on cannabis use was available for 84 users at baseline and at 3 months data on cannabis use were available for 29 users. Data on readiness to change at baseline and cannabis use at 12 months were available for 27 of the 84 baseline users. Information on readiness to change at 3 months and cannabis use at 12 months was available for 14 of the 29 cannabis users (Table 7.1).

Table 7.1 Number of participants with data on cannabis use at 12 months and readiness to change at baseline and 3 months

	Cannabis users	Completers of RR/ Cannabis use at 12 months	Completers of RCQ-TV/ Cannabis use at 12 months
Baseline	84	27	-
3 months	29	14	14

7.4 Measures

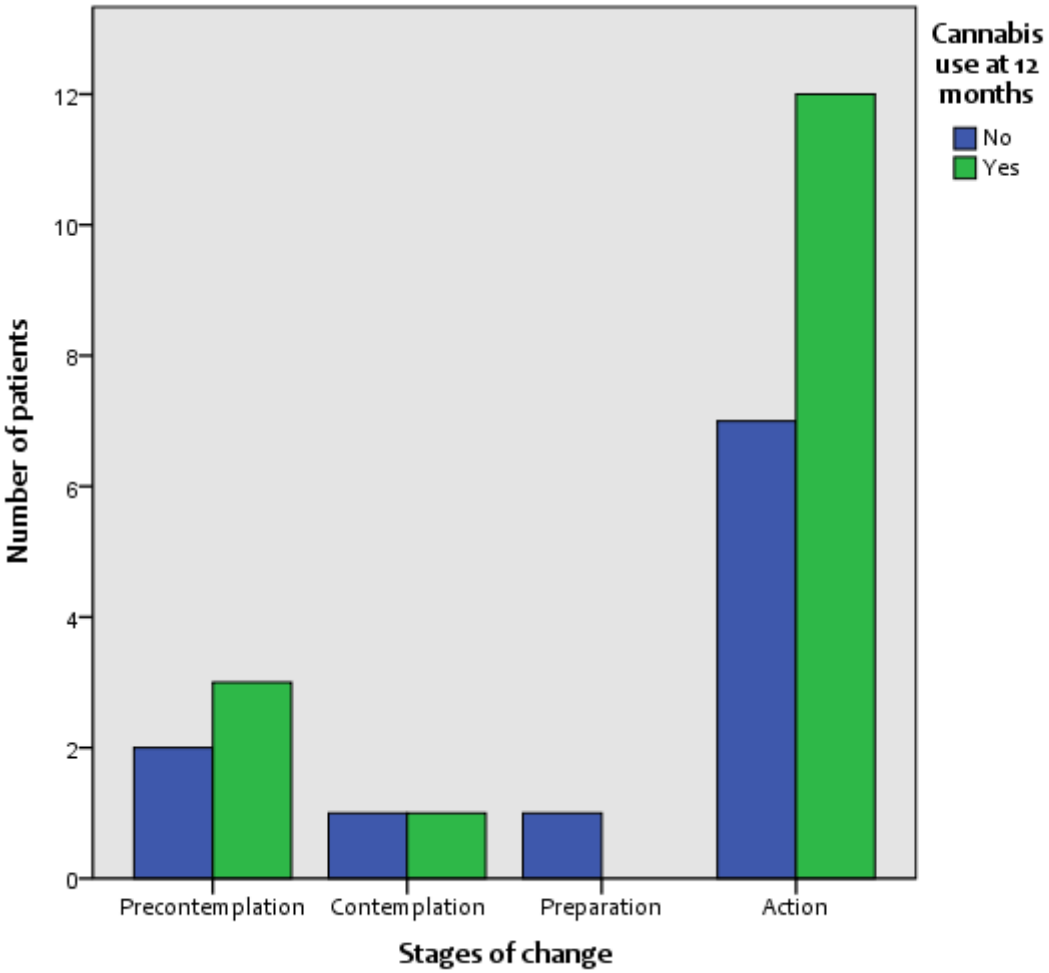
Cannabis use at baseline, 3 months and 12 months was assessed by the CEQ_{mv} (Chapter 4; section 4.2). Cannabis use at baseline was defined as use at least once in the last year. At 3 and 12 months cannabis use was not strictly defined within a particular time frame but participants were invited to report use or non-use around the point of follow-up assessments. Non-use was defined as not having used cannabis in the last year for baseline assessments and not using cannabis around the time of each follow-up assessment. Readiness to change at baseline was measured by the Readiness Ruler (RR) and at 3 months by the RR and the Readiness to Change Questionnaire- Treatment Version (RCQ-TV). Due to the length of the baseline data collection schedule, it was decided to use the RCQ-TV for assessment of readiness to change only at 3 months.

7.5 Analyses and results

Due the small sample size it was not possible to statistically test the a priori hypotheses.

According to the RR, of the 19 patients at the action stage at baseline, 12 were using cannabis at 12 months and 7 were not. Of the 2 patients who were assigned to the contemplation stage, 1 was still using cannabis at 12 months and 1 had stopped. Five patients chose the pre-contemplation stage at baseline, of which 3 were cannabis users at 12 months and 2 were non-users. One patient at the preparation stage was not using cannabis at 12 months (Figure 7.1).

Figure 7.1 Stage of change allocation at baseline according to RR and cannabis use at 12 months

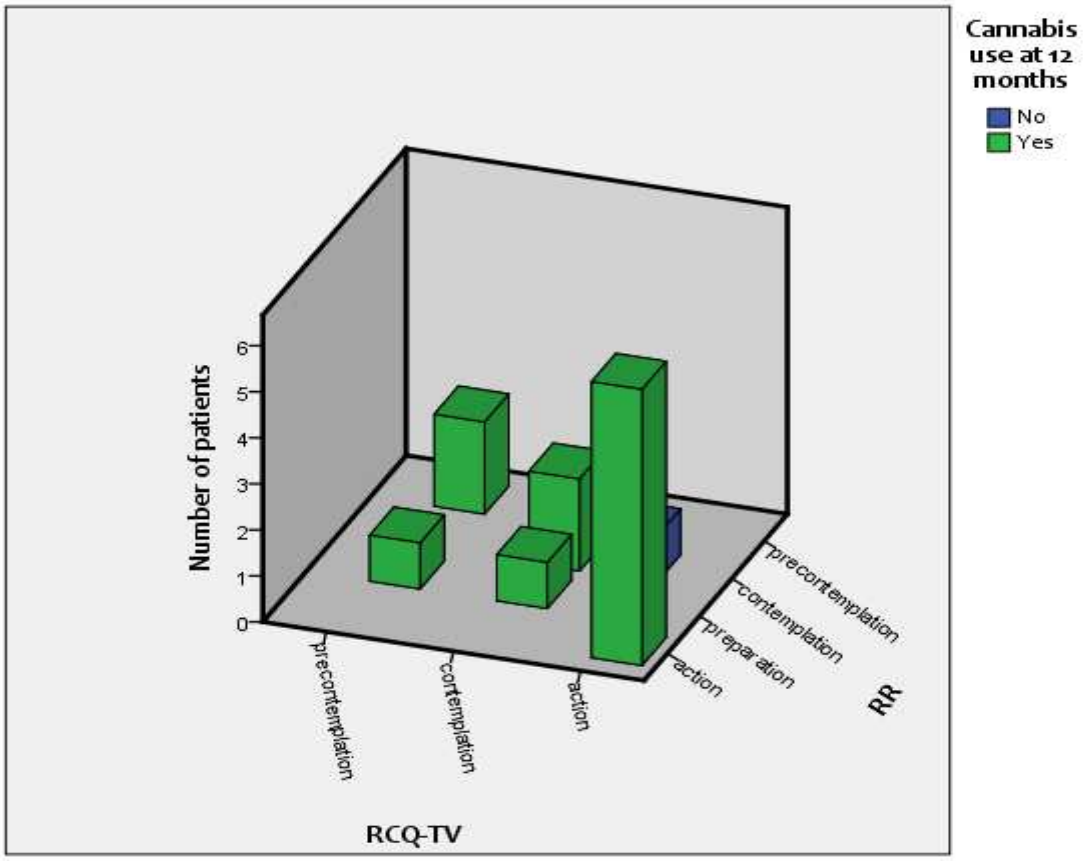


At 3 months the RR and RCQ-TV were used to assess readiness to change cannabis use in 14 cannabis users. Only one was a non-user at 12 months (Figure 7.2).

Eleven patients were assigned to the same stage of change by both questionnaires. Seven patients were assigned to the action stage, 2 patients to the pre-contemplation stage and 2 patients to the contemplation stage.

Assignment to stage of change was not consistent for 3 patients. One patient chose preparation with the RR and contemplation with the RCQ-TV, another patient was assigned to contemplation with the RR and action with the RCQ-TV (non-user) and one patient chose preparation with the RR and pre-contemplation with the RCQ-TV.

Figure 7.2 Stage of change allocation at 3 months according to RR and RCQ-TV and cannabis use at 12 months



Cannabis users at 12 months

Preparation (RR) and Contemplation (RCQ-TV) - 1 patient

Preparation (RR) and Pre-contemplation (RCQ-TV) - 1 patient

Contemplation (RR and RCQ-TV) - 2 patients

Pre-contemplation (RR and RCQ-TV) - 3 patients

Action (RR and RCQ-TV) - 6 patients

Cannabis non-user at 12 months

Contemplation (RR) and Action (RCQ-TV) - 1 patient

7.6 Summary of findings

It appears that the majority of users (19/27) were assigned to the action stage at baseline but more than half of them (12/19) were using cannabis at 12 months. The pre-contemplation, contemplation and preparation stages seemed to be much more associated with cannabis non-use. At 3 months a similar pattern was observed; all patients in the action stage by the RR were cannabis users at 12 months. The only patient to report non-use at 12 months had been assigned to the action stage by the RCQ-TV and the contemplation stage by the RR indicating some inconsistency in stage allocation by the two measures and showing small evidence for the RCQ-TV in predicting behaviour change more accurately than the RR. The lack of sufficient numbers to statistically test the hypotheses makes it difficult to draw robust conclusions but first impressions suggest uncertainty about the association between readiness to change and cannabis use outcomes.

7.7 Discussion

This chapter described a naturalistic design that examined readiness to change at baseline and 3 months and cannabis use outcome at 12 months. Due to the low number of patients who completed the readiness to change measures and had been assessed on their cannabis use at 12 months, it was not feasible to perform a statistical analysis. To our knowledge, this is the first study to attempt an investigation of readiness to change as a measure of cannabis use outcome in patients with psychosis so the results can only be compared against the limited research on readiness to change substance use in co-morbid populations.

Individuals, and even patients admitted to drug or alcohol programs, vary widely in their readiness to change (DiClemente and Hughes, 1990). Nevertheless, low levels of motivation to change substance using behaviour have been observed in a variety of treatment settings. Ziedonis and Trudeau (1997) found that in 224 dually diagnosed outpatients with schizophrenia-spectrum and substance use disorders, 50% were in the pre-contemplation stage, 2% in contemplation, 8% in preparation and 4% in action. In contrary, present findings showed that the majority of users at baseline and 3 months were assigned to the action stage. Differences in sample size and diagnosis are very much likely to have contributed to this discrepancy. However, due to the paucity of research, it

is not possible to exclude the possibility that there is something particular about cannabis use or the way we measure readiness to change in patients with psychosis that has led to such inconsistencies.

Contrary to evidence that higher readiness to change leads to lower rates of substance use (Zhang et al, 2006; Carey et al, 2002), present findings show that more patients in the pre-contemplation rather than the action stage were not using cannabis at 12 months. However, neither of the previous studies reported specific results for cannabis and focused on reduction in use rather than abstinence. Cannabis exposure was also not specified in this sample whereas previous studies had used rigorous methods of classifying patients according to frequency and/or abuse and dependence criteria. Sample recruitment has not been widely standardized with patients in dual diagnosis programs (Ries and Ellingson, 1990; Velasquez et al, 1999) to patients with primary schizophrenia-spectrum disorders (Carey et al, 1999b) included in the analyses. Similarly, some studies included patients from treatment-seeking populations (Pantalon and Swanson, 2003). The aforementioned discrepancies are likely to also obscure any meaningful comparisons between studies that reported results similar to the present findings. Pantalon and Swanson (2003) and Ziedonis and Trudeau (1997) found that patients with high motivation were not enrolled in treatment and those with low motivation were more likely to adhere to their treatment programs respectively, but neither of these studies collected data on substance use outcomes.

Measures of readiness to change have not been developed with dual-diagnosis populations in mind and so far very few studies have evaluated motivational assessments in co-morbid populations. Evidence for the validity and reliability of staging algorithms, the most widely used measures in assessing motivation to change in primary substance users, cannot be generalized to support their use in dually diagnosed patients. A study of co-morbid substance users found that allocation to different stages was consistent with predictions from the Transtheoretical Model (Prochaska and DiClemente, 1983) but distinctions between the stages were not as clear (Belding et al, 1996). Convergence was also low between an algorithm and the URICA; only 31% of the cases were allocated to the same stage (Belding et al, 1996). Additionally, the 4-

factor structure of the URICA was replicated and was shown to have good concurrent validity in one study with dually diagnosed patients (Velasquez et al, 1999) but not in another (Pantalon and Swanson, 2003). In 2003, Carey and colleagues examined the reliability and validity of a self-report algorithm in a population with co-morbid diagnoses and reported that it can be extended to the assessment of patients with severe mental illness. However, several study limitations raise concerns over the algorithm's applicability. It was the aim of this study to evaluate the effectiveness of the RR and the RCQ-TV in assessing readiness to change cannabis use in patients with psychosis. They are both recently developed measures that have only been validated for use with primary substance users as all previous instruments. It would have been of research and clinical value to compare two different instruments – a short, 4-point scale and a longer, more comprehensive questionnaire. Due to the high attrition rate their utility in assessing readiness to change cannabis use in psychotic populations was not validated and only general observations were drawn.

There was concern that the lack of the preparation stage in the RCTQ-TV would have made any comparisons between the two instruments impractical and initially it was aimed to group the stages into readiness (action) and non-readiness (pre-contemplation, contemplation and preparation) to prevent inconsistency although this distinction is arbitrary as previous research has classified motivation differently; low motivation included pre-contemplation and contemplation and high motivation included preparation, action and maintenance (Ziedonis and Trudeau, 1997). Although low completion rates did not allow for any type of re-classification, it appears that the difference between the instruments has not interfered with assignment to stage of change with high convergence between the two, as 11 of the 14 patients were allocated to the same stage. The patient who was assigned to contemplation by the RR and action by the RCQ-TV was the only one not to be using cannabis at 12 months but it would be very hasty to conclude that the predictive validity of the RCQ-TV is higher than that of the RR based on this observation only.

Regardless of stage allocation, rates of cannabis use were high at 12 months. The majority of baseline users (16/27) were using cannabis and 13 of the 14 3-month users reported cannabis use at 12 months. Clinical and demographic

characteristics that could have independently contributed to persistent cannabis use and accounted for the high number of users at 12 months were not taken into consideration due the lack of statistical ability for this investigation. The cross-sectional study design also did not allow for longitudinal data to be collected. This could have affected the results in two ways: a) frequency and amount of cannabis use might have varied between the 3 time points influencing changes in motivation as well as cannabis use outcomes at 12 months and b) readiness to change is a dynamic and fluctuating process and assessment of cannabis use outcomes based on evaluation of readiness to change at one time-point only might not be representative. Repeated measures of motivation as well as cannabis use might be more accurate when assessing the association, or lack thereof, between readiness to change and cannabis use outcomes. Finally, cognitive processes needed to accurately complete a self-report readiness to change measure as well as move through the stages and undertake activities to sustain behavioural change might not operate in a similar manner in patients with a primary substance use problem and patients with co-morbid conditions. Deficits in memory, attention and executive function observed in patients with schizophrenia might compromise the accuracy with which they can report motivational intentions (Buchanan et al, 2005) as well as interfere with developing and following a sustainable goal to reducing or quitting cannabis (DiClemente et al, 2008). However, neuropsychological studies have reported that patients with co-morbid psychosis and substance use perform better at cognitive tests than non-using psychotic patients (McCleery et al, 2006). If patients with psychosis who use cannabis were at a cognitive disadvantage, we would have expected to observe some discrepancies in the completion of the two questionnaires. A short 4-point scale would be less cognitively demanding than a 15-item questionnaire with complex motivational constructs, which would have led to inconsistencies of stage allocation but this was not observed. Similarly, motivation was not more closely associated with cannabis use outcome by either instrument. However, this could mean that even more simple motivational concepts as expressed in the RR prove challenging to patients with psychosis hence the consistent lack of association between readiness to change and cannabis use outcome across the questionnaires.

7.8 Summary

This chapter presented the results from a naturalistic assessment of readiness to change at baseline and 3 months and cannabis use outcomes at 12 months. No clear pattern of association between readiness to change and cannabis use outcome was observed through either the RR or RCQ-TV. The low completion rates did not allow to statistically test the hypotheses. In the next and final chapter, the main findings and a summary of the chapters will be presented together with a general discussion on strengths and limitations and future directions.

Chapter 8 - General Discussion

8.1 Synopsis

In this chapter the findings from each of the studies conducted to test the six main hypotheses are summarized together with the basic demographic and clinical characteristics of the sample at baseline. The main weaknesses of the PUMP study as well as the thesis are reviewed. The main finding was that cannabis use was not associated with total or positive PANSS scores at 12 months, contributing to the evidence base that cannabis use does not affect prognosis in recent-onset psychosis. Cannabis use was associated with other drug use at baseline but this could not be investigated at 3 and 12 months. Cannabis users endorsed enhancement and social reasons as the main motivators for their use further supporting an 'alleviation of dysphoria' model and providing little evidence for the self-medication hypothesis in its original form. Statistical analysis of readiness to change as a measure of cannabis use outcome was not feasible but preliminary investigation showed that stage of change allocation at baseline and 3 months was not associated with cannabis use at 12 months. It was not possible to investigate the validity of the RR and the RCQ-TV in measuring readiness to change in patients with psychosis. The potential research and clinical implications of these findings are discussed.

8.2 Summary of main findings

General characteristics of the baseline sample and differences between participants and non-participants as well cannabis users and non-users were described in Chapter 4. No differences were noted between participants and non-participants. The majority of patients were in their late twenties, male, of white ethnicity, with vocational or professional qualifications and currently unemployed, single but living with others. Psychopathology was low with mean total PANSS scores in the lower end of the moderately ill category and no patients were in the severely ill group. Low rates of stressful events and high medication adherence were reported. High rates of lifetime and current tobacco and alcohol use were observed as well as high rates of other lifetime illicit drug use. Over half the patients reported current cannabis use. Cannabis users were

more likely to be younger, male and living alone. They also reported higher total and positive PANSS scores than non-users and more stressful events. Cannabis users were also more likely to report lifetime and current tobacco, alcohol and other drug use than non-users.

The aim of the study in Chapter 5 was to investigate the association of cannabis use and mental health outcomes at 12 months and the association between cannabis use and other illicit drug use at baseline, 3 months and 12 months. Using a series of cross-sectional assessments, it was firstly observed that cannabis use was not associated with total PANSS scores at 12 months. The only variable associated with 12-month total symptom severity was baseline total PANSS scores. The second finding was that although cannabis use was independently associated with positive PANSS scores at 12 months, in a multivariate analysis baseline PANSS scores remained the only variable significantly associated with 12-month positive PANSS scores. These results do not support the evidence base that cannabis use affects prognosis in patients with psychosis. The small sample size, low psychopathology rates and lack of cannabis exposure classification might have contributed to these negative findings. Thirdly, cannabis use at baseline was associated with other illicit drug use and this remained significant after adjusting for potential confounders. This was not possible to test at 3 and 12 months due small sample size. The association between cannabis and other drug use in patients with psychosis has not been investigated before but these findings suggest there is a robust relationship that warrants further examination.

In the study in Chapter 6, the aim was to assess the reasons for cannabis use at baseline, 3 months and 12 months. In a cross-sectional design, patients endorsed enhancement as more important than any other reason at all 3 time points with social motives following closely. In a post-hoc mixed model analysis it was observed that patients felt much more strongly about their reasons for cannabis use at baseline than at 12 months but this difference was not found in comparisons between 3- and 12-month ratings. The use of a validated measure to assess reasons for use and the large sample size and inclusion of in- and outpatients contribute reliable evidence to support enhancement and social

reasons for use rather than the traditional self-medication hypothesis adding to the existing evidence base of similar findings.

The aim of the study in Chapter 7 was to investigate readiness to change at baseline and 3 months as a predictor of cannabis use outcomes at 12 months. The utility of two instruments in assessing readiness to change as a measure of cannabis use outcome was also examined. The lack of sufficient numbers did not allow for statistical testing in this series of naturalistic assessments but preliminary results showed that high readiness to change was not associated with cannabis non-use. The majority of cannabis users were assigned to the action stage at baseline but more than half were using cannabis at 12 months. At 3-month assessments of readiness to change, all users in the action stage were using cannabis at 12 months. The Readiness Ruler and Readiness to Change Questionnaire- Treatment Version could not be validated for assessing readiness to change cannabis use in patients with psychosis.

8.3 General limitations

These studies, though both consistent with some previous research and delivering some novel findings, were not without limitations and the weaknesses of the PUMP study in general and a summary of the biases in the thesis methods will be addressed here.

8.3.1 Limitations of the PUMP study

Some issues with the present investigation stem from the fact that it was nested within a larger cohort study, the PUMP study. PUMP recruited participants from a number of inpatient and outpatient settings covering large catchment areas, included an intensive study battery and employed a high number of research workers that delivered the assessments. Within a limited time frame in the context of a smaller study, it would not have been otherwise feasible to reach such a wide range of patients or collect this amount of data without the enhanced resources available. However, the magnitude of the study produced some methodological weaknesses.

Length of assessments

The length of assessments administered to patients (around 4 hours) meant that many were unable to complete the assessments at baseline or refused to return for follow-up investigations. Willingness to complete assessments or continue in the study may have been further compromised by the inclusion of biological assessments that some patients might have found intrusive (blood collection) that due to the fasting nature had to be conducted first. Completion rates from one measure to another varied widely within each time point and attrition rates were very high. Consequently, statistical power was considerably reduced and analyses that were required to test the hypotheses were unavailable for Chapter 7. Every effort was made to complete measures as quickly and in as few sessions as possible but in some cases delays were necessary due the large study battery. Although it was more feasible to complete assessments quickly and efficiently in inpatient facilities, patients were sometimes discharged from hospital in the middle of the battery completion. Conducting assessments with outpatients was more challenging especially when circumstances such as work, study and child-care increased delays. Symptom severity measures could have been affected by these delays as psychopathology may change significantly throughout the course of assessments. Similarly, cannabis use could have been affected by availability due to changes in inpatient or outpatient status and symptom severity. It was not possible to guarantee that measures of symptom severity and cannabis exposure were collected at the same time and this may have added statistical noise to the data utilised for this thesis.

Multiple researchers

Assessments were delivered and scored by multiple researchers, which may have affected ratings. Although steps were taken to ensure researchers were thoroughly trained in each measure with repeat training sessions available throughout the course of the study and relevant experts available for support and advice when needed, it is likely that differences between raters existed particularly for less structured instruments such as the PANSS or for cannabis exposure assessments. This might have caused a systematic effect and under- or

over-estimated symptom severity and cannabis exposure influencing the direction of the results.

Selection bias

The differences between completers and non-completers of measures have been examined where necessary throughout the thesis but it is important to note that a wider selection bias might have occurred in the PUMP study. It is not possible to ascertain how patients who agreed to take part in the study differed from those who refused. It is very likely, as also evident from the low psychopathology rates across the sample at baseline that patients who were severely ill were not able to consent and are underrepresented in the PUMP study and the thesis.

Design

Finally, a cohort design was chosen as it allows for multiple explanatory factors and multiple outcomes to be measured. It also provides a temporal sequence of exposure and outcome, which would not have been possible if a case-control design was chosen. Temporal causation would not have been determined through a one-time cross-sectional design. A randomised-controlled trial design wouldn't have been feasible either, as it would be unethical to purposefully expose individuals to lifestyle habits (i.e. poor diet, substance use) that are known to have detrimental health effects. However, the cross-sectional pattern of data collection at the 3 time points did not allow for longitudinal, repeated assessments into changes in psychopathology, cannabis use, reasons for use and readiness to change to be conducted.

8.3.2 Biases in thesis methodology

The strengths and weaknesses of each investigation have been addressed in respective chapters and a summary of the main systematic and residual biases are discussed in this section.

One of the main sample characteristics that might have systematically affected the results of this study is the low psychopathology rate. This observation might have underestimated the effects of cannabis use on symptom

severity at 12 months especially because patients with more severe total and positive psychopathology at baseline were less likely to complete the PANSS scale at 12 months. It could also have affected the reasons patients endorsed for their cannabis use. With the inclusion of less severely ill patients, we avoided the potential bias from patients already having failed in self-medication attempts and being less likely to choose such reasons as important but might have created another confounder. If patients were relatively well, they might have endorsed other reasons as more important simply because their recovery has allowed them to enjoy cannabis in ways otherwise not possible had they been very psychotic. The consistency of our findings with previous research indicates that this systematic bias might not have influenced the results but is still essential to consider it.

The possibility of potential confounding that was not included in the analyses should be considered carefully. The high attrition rate prevented further classification of cannabis exposure based on quantity, frequency, duration of use before presentation to services or further categorization of use, abuse and dependence. Differences in psychopathology between cannabis groups might have been missed in this study, although research that has reported significant effects of cannabis use on psychotic symptoms as well as those studies that failed to observe a relationship have not always classified cannabis exposure based on the aforementioned criteria (Addington and Addington, 2007; Stirling et al, 2005). The low rate of patients endorsing self-medication reasons as important might have been due to infrequent cannabis use that was not possible to consider. However, not all studies that examined different patterns of use reported a greater incentive to relief positive symptoms or medication side effects by patients using cannabis at higher frequency or greater amounts (Schaub et al, 2008).

The effects of antipsychotic medication were not controlled for in this study and so it was not possible to test whether differences in 12-month follow-up psychopathology ratings were related to the type or level of medication. This did not appear necessary in the present study as high medication compliance was observed and further confirmed by the low psychopathology rates and no differences were found on medication adherence between cannabis users and

non-users at baseline. Different antipsychotics might have influenced the endorsement of reasons for cannabis use. Previous research presented mixed findings with patients on typical antipsychotics reporting cannabis use to counteract the effect of 'being slowed down' more often than those on typical antipsychotics (Addington and Duchak, 1997). However, patients on atypical antipsychotics only chose to 'reduce boredom' as a reason for use more often than healthy controls (Schaub et al, 2008). The consistency of the present findings with previous research makes it unlikely that this residual bias had an effect on the results.

8.3.3 Summary of strengths and limitations

The strengths of this thesis included strict criteria for definition of first-episode psychosis and cannabis use and the inclusion of inpatients and outpatients from all psychotic diagnoses. Another advantage has been the systematic adjustment for potential confounders identified from baseline comparisons between cannabis users and non-users. Urinalysis to corroborate self-reported cannabis use at the 3 time points has added validity to the investigations. Similarly, validated questionnaires were used for assessing effects of cannabis use on symptom severity and examining reasons for cannabis use in psychosis. The main limitations of the study were high attrition rates; low levels of psychopathology; lack of cannabis exposure classification and lack of longitudinal assessments through repeated measures.

8.4 Research implications

Effects of cannabis use on established psychotic disorders and its association with other drug use

No consensus has been reached as to whether cannabis independently affects the course of psychotic disorders. Some evidence exists that cannabis use exacerbates psychotic symptoms in patients and affects prognosis and recovery. However, some research, including the present, has not found an association between cannabis use and psychotic outcomes. No research has examined the association of cannabis use with other drug use in patients with psychosis. In this

section suggestions for future research aiming to examine these investigations are discussed.

Firstly, diagnostic criteria for psychosis and classification of first or recent-onset need to be standardized. Studies vary in their definitions of inclusion criteria and some have excluded bipolar patients or those with substance-induced psychosis from their analyses. The influence of cannabis use on these patients might differ from those with a schizophrenia-like presentation although Hinton et al (2007) did not observe such a distinction. Studies such as the present, which have included all psychotic diagnoses, provide valuable information to the evidence base but research on sub-groups of psychotic patients would contribute to the findings on the effects of cannabis use by highlighting issues that might otherwise be ignored. As Zammit et al (2008) observed, studies of patients with schizophrenia or related spectrum disorders consistently report worse outcomes in those who use cannabis. It would also be beneficial to avoiding observer bias if measures of symptom outcomes are masked to cannabis exposure (Grech et al, 2005; Linszen et al, 1994). In order to prevent overestimation of causal effects, adequate adjustment of confounders should be carried out both from baseline comparisons between using and non-using groups as well as potential biases that have been identified in previous research. This has not been systematically adopted and might partly explain the inconsistent findings.

Another challenging issue for future research is the classification of cannabis and other drug use exposure. Some studies, including ours, failed to categorize patients based on frequency, intensity or duration of use and might have underestimated the true effect of cannabis and its association with other drug use, as this failed to be observed at 12 months. Similarly, a distinction between use, misuse and abuse should be applied wherever possible using validated methods. When distinction with respect to intensity was made, heavy cannabis users appeared to have poorer outcomes with more and earlier relapses (Linszen et al, 1994). Duration of use before presentation to services is also important, as Green et al (2004) observed that lifetime cannabis use was more strongly associated with worse outcomes although current cannabis use disorders were rare in their sample. Collecting this information from multiple

sources instead of solely relying on self-report might procure added validity and avoid recall bias. Urinary drug screens could assist in ascertaining cannabis and other drug use exposure but in order to establish the functional impact necessary to make a diagnosis, serum drug screens should also be analysed, whenever possible. Variations in potency of cannabis preparations and amounts metabolised can only be determined through these biochemical investigations.

Finally, the choice of study design and sample size will undeniably influence the validity and generalizability of results. Most research so far has inadvertently emphasized the problems with recruiting and retaining patients with co-morbid cannabis use and psychosis. Low completion and high attrition rates are common in research with this population. This unintentionally dictates the amount of information collected and the possibility of adjustments in analyses. Cross-sectional studies have the benefit of not requiring frequent assessments that patients might find time-consuming and intrusive but as demonstrated in the present study this does not necessarily prevent attrition. Of course longitudinal studies with repeated measures of psychopathology, exposure to cannabis and other substances and baseline comparisons on function, illness severity and other factors known to affect psychotic outcomes would be the ultimate paradigm. However, attaining such levels of methodological quality is not an easy task.

The ideal or gold standard study cannot be realistically achieved and I believe that future research should acknowledge these inherent limitations. What can be accomplished is consistency within these weaknesses. Whether studies are large or small, cross-sectional or longitudinal adhering to pre-defined standardized criteria will improve validity. Sometimes a study will settle for a smaller sample size in order to collect more data and other times a larger study will have to negotiate an intensive study battery in order to retain higher patient numbers at follow-up but the more of each that we have the more likely a certain pattern of the effects of cannabis use on psychotic outcomes will eventually become apparent.

Reasons for cannabis use in patients with psychosis

It has been widely shown that patients with psychosis use cannabis for its enhancing and social effects rather than to relieve illness-related symptoms thus providing little support for the self-medication hypothesis. A few methodological problems that might question the validity of such findings as well as inherent issues in the assessment of motivations for cannabis use are discussed in this section together with recommendations for future research.

The major methodological inconsistency that has been observed is the lack of standardized instruments for the assessment of reasons for cannabis use in psychosis. The present study overcame this limitation by utilising an instrument that has been validated in patients with psychosis but most studies used predetermined lists. Besides the suggestibility bias that might arise through the use of such scales (Kot and Serper, 2002), it does not appear that any two studies used the same lists. In the future, an attempt should be made for research to utilize validated instruments in order to facilitate the generalizability of results.

Diagnostic and inclusion criteria for psychosis and cannabis exposure classification should also be utilized in a standardized manner. Previous studies have only included outpatients in an attempt to prevent bias from already failed self-medication attempts but the present study showed that reasons remain largely similar between inpatients and outpatients by including both groups. Studies comparing reasons in patients with varying degrees of psychopathology would be beneficial in establishing whether failed self-medication attempts in severely-ill groups or the relative remission of patients with fewer symptoms influence the endorsement of some reasons more than others. Inclusion of any psychotic diagnosis should also be employed. Most studies so far have examined reasons for use in patients with schizophrenia-spectrum disorders only but limited evidence from two studies as well as the present shows that populations with psychotic disorders endorse the same reasons and findings need to be replicated. Cannabis classification would highlight any effects that varying frequency or quantity of use might independently have on reasons for use as it has been shown that heavier use is sometimes associated with endorsement of medication-related reasons.

Finally, pharmacological treatment should be taken into account when examining reasons for cannabis use in patients with psychosis. For evidence to support that relief from side effects is not an important reason for use, it would need to assume that all patients experience similar medication side effects at the same rate and extent. Since this is not clinically possible, future research should be conducted on investigating potential differences in the reasons for use between patients on typical and atypical antipsychotics as well as those on anxiolytic or antidepressant regimes. For instance, are patients treated with one type or a combination of neuroleptics more likely to report endorsement of particular reasons than other treated patients and do these differ from those who are medication-free?

Besides the aforementioned methodological issues that future research should aim to resolve, I would also like to present some thoughts and criticisms on the nature of assessing reasons for cannabis use and why it might already be problematic.

Self-reported reasons for cannabis use are subject to recall bias and might be further unreliable because they depend on the experiences that occur while under the influence of the substance. When these experiences do not live up to the expectations of actual use additional complications in assessments are inevitable. On the other hand, it would be impossible to assess reasons for use through third-party observations. Relief of positive symptoms and medication side effects are invariably grouped and assessed as one reason but intuitively the attempt to cope with hallucinations or delusions is distinctly different from efforts to reduce medication side effects. Even in the case that these two groups of reasons can be reliably assessed as one category, how certain are we, as researchers and clinicians, that patients with psychosis can observe and deliver a clear report of what constitutes a medication side effect? Similarly, relieving anxiety or depression are recurrent themes in what motivates patients with psychosis to use cannabis but it is quite difficult to establish whether these symptoms are related to disease process or medication side effects. Inviting patients to make this distinction is even more challenging and unlikely to generate reliable responses. Investigation of reasons for use in the wider context of potential risk factors for cannabis use has also not been conducted. Most

studies on cannabis use and psychosis have been over-represented by young, male patients but differences based on gender and age have not been examined.

Findings in favour of the traditional self-medication hypothesis have not been observed but evidence for the 'alleviation of dysphoria' version of this hypothesis appears to be consistently reported. This presents further support for the secondary substance use disorder model, which postulates that substance use disorders are caused by severe mental illness (Mueser et al, 1998). Although patients endorse reasons that reflect symptom relief they are not related to positive symptoms but rather to alleviation of negative affective states. Regardless of methodological weaknesses that future research should attempt to settle, it is unlikely that this consistency in findings across studies has been fortuitous. Patients with psychosis are most likely to be using cannabis for the same hedonistic motives found in reasons for use by the general population. Nevertheless, there are some challenges with the nature of assessing reasons for use that could be revisited and resolved.

Readiness to change cannabis use in patients with psychosis

Three main issues have arisen from the examination of readiness to change as a measure of cannabis use outcome: a) no research has been previously conducted in this area with most studies investigating readiness to change in primary substance users or co-morbid populations but without special focus on cannabis or psychosis, b) instruments developed to measure readiness to change substance use have not been validated for use in patients with psychosis and c) preliminary examination of the association between readiness to change and cannabis use in this study did not find that higher motivation is related to cannabis non-use. The future of research examining the validity of readiness to change to predict cannabis reduction or cessation needs to take into account all the aforementioned 'gaps'.

Since there is a lack of studies reporting on this association in patients with psychosis that use cannabis, a starting point would be to determine basic methodological matters a priori. Results from the other two investigations in the present study have highlighted the importance of utilizing strict diagnostic criteria for psychosis and cannabis exposure. Longitudinal assessments would be

more appropriate than a cross-sectional design as fluctuations in both cannabis use and readiness to change might influence cannabis use outcomes and assessment of either at one-time point only might not accurately reflect later behaviour change.

Before getting to the stage of conceptualising and realising a research study to measure any association between motivation and changes in cannabis use, a suitable instrument to assess this relationship needs to be developed. It's likely that one of the numerous scales that have been developed for primary substance users is suitable for use in patients with psychosis but we were not able to reach such a conclusion. Cognitive processes that are required to complete such assessments might differ between substance users and patients with co-morbid conditions and this would need to be considered when developing the scale.

We did not observe any evidence that readiness to change explains cannabis use outcomes. This is likely due to the low numbers of completed assessments and lack of statistical analysis. However, a key question remains; if intention to change appears to be prominent in periods following first presentation but still fails to relate to later behaviour change, is this occurring because we have not categorized or evaluated motivation accurately or are other factors more likely to influence changes in cannabis use? Clinical and demographic characteristics that could independently contribute to cannabis use were not controlled for in this investigation and future research should ensure to at least consider age, gender, and psychopathology as possible explanatory variables of changes in cannabis use. Social and environmental circumstances could also separately influence changes in cannabis use.

Observations by Spencer et al (2002) emphasize the likely association between reasons for use and readiness to change. They found that patients who used cannabis to cope with unpleasant affect had a higher readiness to change than those who endorsed other reasons. They also showed that increase in psychotic symptoms led to increase in motives for use, which in turn led to increased dependence. Reasons for use are the means by which psychotic symptoms affect problematic use of cannabis. Effects of psychotic symptoms on cannabis use are likely to be mediated by the motives that sustain the use and

influence readiness to change. Research should focus on investigating the reasons for cannabis use that patients are aware of and the patterns of use that are related to those reasons (Spencer et al, 2002).

8.5 Clinical implications

So far we have reported on the effects of cannabis use on psychotic outcomes but this is only one aspect of illness trajectory and other elements of general functioning that might be affected by persistent use. Preceding psychotic symptoms seem to be much stronger and clinically important predictors of future psychotic symptoms but global functioning and mood are also important in sustaining remission from psychosis. Since cannabis use has been associated with smaller improvements in these areas (Hinton et al, 2007), it should be widely discouraged and efforts to reduce harmful effects from cannabis should remain a priority particularly if poly-drug use is present. Clinicians should provide information about the risks of cannabis and other drug use. Developing treatment strategies to prevent cannabis use is essential, as it appears to be at least a stressor for psychotic relapse.

Comprehensive early psychosis treatment should be paramount. There are optimistic observations that indicate a naturalistic reduction in substance use over time by patients who present to services for the first time (Addington and Addington, 2007; Hinton et al, 2007). It appears that there might a window of opportunity for encouragement and intervention but it will be a challenge for effective relapse prevention to develop and implement effective treatment strategies for co-morbid psychosis and cannabis use (Ley and Jeffery, 2003; Wade et al, 2006).

Despite the negative findings from the present study, a large body of evidence still suggests that cannabis use is likely to trigger relapse in this population and it is still important to develop strategies to reduce or eliminate motivators that sustain it. Since patients appear to largely use cannabis to relieve negative affective states such as depression and anxiety rather than positive psychotic symptoms, treatment should be modified to attempt alleviation of such states through psychological and pharmacological intervention. However, this cannot be adopted independently as treatment for the psychosis would have

to be applied concurrently. The purpose of examining the reasons for use should not be to reach a finite all-inclusive treatment strategy but to recognise individual preferences and target interventions accordingly. Awareness of patients' reasons for cannabis use would give clinicians a theoretical basis for planning psychotherapeutic interventions as well as pharmacological treatments with a view to target positive symptoms and reduce side effects, which for some patients might still be strong motivators in sustaining their cannabis use.

Challenging the belief in each motivator and providing alternative means of achieving psychological effects from cannabis use should be an essential part of treatment. Patients who use cannabis for social reasons are likely to benefit from assertiveness training giving them the opportunity to explore the patterns of such social use, choosing social alternatives, identifying high risk situations and feeling socially comfortable in the absence of cannabis. Exploring perceived effects of cannabis use and challenging positive expectations might be advantageous to patients whose primary motive is psychological enhancement. Goal planning and lifestyle strategies should comprise the core treatment. For the minority of patients who use cannabis to relieve positive symptoms and medication side effects psycho-education would be a valuable starting point of intervention. There needs to be focus on raising awareness of mental health problems, recognising their presence and choosing appropriate techniques to overcome them. Exploring perceived expectations of cannabis use and actual benefits might help to break the cycle of dependence as would relapse prevention training. It would be of benefit to also consider alternative treatments to ease positive symptoms. As Gregg et al (2007) propose, patients who use drugs primarily for social and enhancement reasons should benefit from interventions such as Motivational Interviewing, whereas those who use drugs primarily for emotional reasons (e.g. negative states) might find Cognitive Behavioural Therapy more beneficial. It is likely that such patient-centred strategies would be helpful to patients with psychosis attempting to reduce or give up their cannabis use.

Knowledge of the reasons that encourage patients to use cannabis may offer clinicians an advantage in effecting change. This would be particularly helpful in cases where subjective experiences of cannabis use are opposite to the

actual motivations. Reflecting this discrepancy back to the patient may help with assisting them to move along the decision ladder and reaching a point of taking action to change.

Identifying the reasons that sustain cannabis use is a complex psychological process. Usually patients endorse more than one reason as pertinent for their cannabis use and so assessment of these motives should be a multidimensional and ongoing process. Reasons for use appear to vary with time and circumstances and so interventions will have to follow a similar pattern. In a case series examining reasons for cannabis use in patients with psychosis from the present study (Kolliakou et al, 2012), observations from clinical assessments appeared to be consistent with the subsequent choice of reasons for use. It is very promising that self-reported reasons for use appear to validate an existing clinical picture as in a clinical setting where standardised measures are not routinely used to assess reasons for use, ongoing observation and active listening can be employed in a non-confrontational manner to identify what sustains cannabis use and offer appropriate treatment. This can also be an effective strategy with patients who are reluctant to openly discuss cannabis use per se.

Co-morbid cannabis use and psychosis is likely to complicate behaviour change and demand multifaceted treatment planning, particularly when patients use other illicit drugs as well (DiClemente et al, 2008). Differential motivation with regards to each condition is likely to exist. Patients might be ready to make changes in their cannabis use but not other drug use and be reluctant to accept responsibility or adhere to treatment for their psychosis. Assisting these patients to contemplate and follow a behaviour change plan is difficult but essential.

Motivation to change cannabis and other drug use in the context of a psychotic disorder needs to be targeted separately as well as part of an integrated process. Clear aims about the specific behaviour change need to be set from the beginning. Is the patient more confident about gradual reduction of use or are they determined to quit altogether? Are they happy to consider a change plan with regards to cannabis or other drug use when they are refusing medication or involvement in psychological treatment for the psychosis? Motivation to change one behaviour does not imply motivation to change

another (DiClemente et al, 2008) and motivation to change is not identical to motivation for treatment (Freyer et al, 2005).

Self-reported readiness to change might not be judged at the same level as clinicians' ratings and this can have important clinical implications. Research has shown that patients with schizophrenia rate themselves at a higher stage of change than they actually are according to clinicians' ratings (Addington et al, 1999) and this might complicate the choice of treatment interventions. Is the discrepancy in stage allocation due to report bias? If patients have difficulty in grasping the essence of motivation or expressing goal setting and following a behaviour change plan, then different ways of assessing readiness to change in clinical settings need to be utilised. Patients might also express higher motivation to change because they lack the ability to make practical evaluations of what a change plan actually involves. When clinicians consider patients' motivation to be over-optimistic, they need to closely re-examine how realistic the goal setting has been and make sure that patients are aware of obstacles and difficulties they will undeniably encounter in the process of cannabis use change and how to best overcome them. A very delicate line exists between discouraging patients who seem unrealistically motivated to change their cannabis and other drug use and encouraging them to openly accept the challenges that come with a behaviour change plan and assisting in resolving them and reaching their goals.

Besides concerns about how accurately motivation can be assessed and how much it can be done to enhance it, clinicians need to acknowledge the existence of a multitude of problems that might affect it. Problems may exist in areas of beliefs and attitudes, interpersonal relationships, social systems and intra-personal conflicts and deficits (McLellan et al, 2000; Ziedonis et al, 2005). These contextual problems often complicate attempts to change behaviour and 'offering multiple resources simultaneously in treating individuals with multiple problems should be as much about motivation and completing the stage tasks for the target behaviours as it is about resolving additional problems' (DiClemente et al, 2008; pp.31).

Finally, the structure of motivational and behavioural interventions depend on the level of readiness to change and stage allocation by the patient. Patients with lower motivation levels might benefit more from structured

programs that provide clear goals and reward participation and engagement, whereas patients at higher stages of change might gain more from reinforcement in assisting to promote the behaviour change that is already being adopted (DiClemente et al, 2008). Clinicians need to accept that motivation is largely about intrinsic processes of problem resolution, goal setting and achievement and what they consider to be a good plan might not reflect patients' aspirations. Reduction of cannabis use with a view to minimize harm should be accepted as an intermediate goal while ensuring that mental stability is achieved before promoting more radical changes. Establishing what stimulates change is essential but it might not be consistent between patients and clinicians.

Although recommendations from this study cannot be made due to the negative findings, a main implication for clinical practice arises from previous research; the need for integration of cannabis-specific treatment in services primarily attended by patients with psychosis. Based on the findings from the current study, the development of personalised interventions, that suit individual needs by establishing the effect that cannabis use has on illness and wider functioning, motivations for cannabis use and readiness to change throughout the course of treatment and thereafter, is also recommended.

8.6 Conclusion

While it is plausible that cannabis interacts with a number of psychological, genetic and neurobiological factors to contribute to the onset of psychosis and worsen outcomes in patients with an established disorder, this study did not observe an effect of cannabis use on psychotic prognosis. Although patients use cannabis mostly because of its enhancing and social effects, some individuals still seek relief of positive symptoms and medication side effects through persistent use and the self-medication hypothesis cannot be invariably disproved. Motivation to change cannabis use in a population of young people already struggling with the effects of a potentially life-intrusive mental health illness would undoubtedly vary but might be amenable to patient-centred treatment. Developing suitable measures to help clinicians assess fluctuations in readiness to change will enable them to choose the appropriate intervention at the right time. Integrated treatment for patients with co-morbid cannabis use and psychosis is unquestionably needed.

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APPENDIX 1 – PATIENT INFORMATION SHEET AND CONSENT FORM

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University of London
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Physical Health and Substance **U**se **M**easures in First Episode **P**sychosis (PUMP)

PATIENT INFORMATION AND CONSENT FORM

What is the purpose of this study?

You are being invited to take part in the PUMP study. Please take time to read the information below and ask any questions if something is not clear. This study overlaps with Genetics and Psychosis (GAP) but there are also some differences. The similarities are that both studies are recruiting the same group of people and collecting similar information about mental health and lifestyles along with blood samples at baseline. The differences are that in PUMP we aim to explore how lifestyle factors (exercise, diet, substance use), genes and prescribed medication affects aspects of your physical health such as weight, cholesterol and sugar levels, and also your mental health over a 12 month period. By combining our resources with the GAP study we aim to reduce duplication of assessments and sampling.

Why have I been invited?

You have been invited to take part in this study because of the nature of the symptoms that you appear to have been experiencing. We are aiming to recruit approximately 600 people.

Do I have to take part?

Participation in the study is voluntary. Your decision to participate (or not) will not affect your health care in any way.

Are there any benefits involved in taking part?

Through our testing and by maintaining contact with you at various points over a 12 month period you will be able to assess your level of physical health. Your care coordinator will also be involved in some of the assessments and will also learn about your physical health status. You will also be helping us to better understand the physical health problems faced by people from the time of their presentation to services with a diagnosis of psychosis. This will enable health care services to provide better care for patients with psychosis and develop better ways of screening for diabetes and risk factors for heart disease such as offering advice about ways to change diet, increase exercise and reducing use of illicit substances.

We will reimburse any travel expense related to your participation into the study.

What will happen to me if I take part?

If you decide to help us with our study, we will ask you to complete a number of measures at the following time points:

1. We will ask you various questions about your symptoms; any side effects from medication; diet; levels of physical activity; use of NHS services, and your views on your health risks. We will then give you a pedometer to wear for up to one week at both baseline and then again at 12 months to tell us how often you are active and the amount of calories you burn in a day.
2. At baseline and 12 months a trained researcher will take a small sample of fasting blood (10mls which is 2 teaspoons) from you using disposable sterile equipment, to check your blood sugar, cholesterol and fat levels and assess your risk for diabetes, heart disease and other related health problems. This will only take a few minutes. You should not eat or drink anything from midnight and we take the blood sample first thing in the morning, ideally at 8am before you eat.

3. To monitor your physical health we ask you for your permission for us and/or your medical team to measure your weight, blood pressure and waist and hip measurements at 2 timepoints (baseline and 12 months), along with finger-pick tests for blood sugar levels when blood tests aren't already scheduled. This will take approximately 15 minutes each time. At 12 months we will repeat the initial assessments to investigate changes over time. We will liaise with you, your care coordinator and your GP to plan the best way of collecting this information and share the sugar and fat level results with your clinical team so that you don't need to do the tests twice. You will also be able to request a copy of the test results.

4. We will also ask you to provide a urine or saliva sample to allow us to screen your drug use. We will not relay any information about the drug screen to the police. This information will be kept strictly confidential within the research team.

The table below summarises points 1-4:

	WHEN WE FIRST SEE YOU (BASELINE)	**12 MONTHS later**
MEASURES TO BE TAKEN	**Fasting bloods** **Blood pressure** **Weight** **Questionnaires** **Urine sample** **Pedometer**	**Fasting bloods** **Blood pressure** **Weight** **Questionnaires** **Pedometer**
WHO BY	**Your Researcher**	**Your researcher**

The study will require approximately 1 hour at baseline and a further 3 hours over the 12 months. Each time you complete the measures required at each visit (baseline and 12 months) you will receive £20 for your time and any travel expenses will be reimbursed.

If you have already taken part in other research at the Institute of Psychiatry, London involving some of the above measures, we will not ask you to repeat them but request your permission to use the existing data.

We will ask your consent for longer-term follow up to contact you or your GP and to view your medical records. This is so that we can see whether your physical health status changes over time, such as your risk for diabetes, or heart disease. We are also requesting your permission to contact you in the future to take part in other studies that you may be eligible for.

Are there any risks involved in taking part?

The risks involved are those of ordinary blood tests such as slight scratch and occasionally a small bruise from where the sample is taken. There is no risk in the collection of urine or saliva.

Will my data be confidential?

All personal information about you will be strictly confidential, unless you agree for some of this information to be shared with your clinical team. Only researchers belonging to the study team, and not external collaborators, will know which sample belongs to whom. All information about you will be kept anonymous so you cannot be identified in any research outcome.

The blood samples will be stored in a secured laboratory for 5 years. Samples will be coded using identifiers, which will be entered on a secure computerized database. The identifiers will not refer to your name or date of birth. All clinical information collected on your sample will be securely held in the Institute of Psychiatry building. Access to the samples and the related information will be restricted to the researchers involved in the study. In case of commercial collaborations only the coded data will be shared. If there is a new study aim that requires further data collection not already covered by this study, this will be subject to review by a research ethics committee.

You are free to withdraw from this study at any point without giving a reason by contacting the researcher whose details are at bottom of the consent form. Withdrawal will not affect your health care.

What will happen to the results of the study?

We will send you a newsletter during the study to outline the project. Then when the project is completed we will send you a general summary of our research through a newsletter and a website under the Division of Psychological Medicine, Institute of Psychiatry (www.iop.kcl.ac.uk).

Who is funding this project?

This study is funded by the National Institute for Health Research (grant number 1049) in the Department of Health.

Who has reviewed the study?

The study has been reviewed by the Mental Health Research Ethics Committee.

Who can I contact for more information?

If you have any questions, please contact Dr Stefania Bonaccorso on 0207 848 5480, or by email at: Stefania.Bonaccorso@kcl.ac.uk

CONSENT FORM

If you have come to the decision of entering the study after carefully weighting the information provided please read and sign this form.

Title of project: Physical Health and Substance Use Measures in First Episode Psychosis (PUMP)

Researcher: Dr Stefania Bonaccorso Institute of Psychiatry

Please tick boxes

1. I have read the information sheet and I have been given a copy. I was given the opportunity to ask questions. I understand why the research is being done and risks involved.

YES NO

2. I agree to give blood samples for research in the above project and give consent for the results of my previous blood samples to be examined by the research team and to be included in the analysis of this study. I understand how the sample will be collected, that giving the sample is voluntary and that I am free to withdraw at any time without giving a reason, and without my medical treatment or legal rights being affected. I understand that I will be contacted in the future to repeat parts of the assessment.

YES NO

3. I request a copy of my blood test results

YES NO

4. I agree to give a urine/saliva sample for drug screening. I understand that giving the sample is voluntary and that I am free to withdraw at any time without giving a reason, and without my medical treatment or legal rights being affected.

YES NO

5. I give permission for the results of my urine/saliva drug screen to be shared with my medical team and GP.

YES NO

6. I give permission for some of my research data to be shared with the medical team. I understand that sharing this data with the medical team will reduce the amount of time and repeat assessments that I undergo.

YES NO

7. I agree to wear a physical activity monitor.

YES NO

8. I agree to take part in a tape recorded interview about my views on my health.

YES NO

9. I give permission for my previous research and medical records to be looked at. This information will be analysed in strict confidence by the research team. Researchers external to the study team and collaborating in this project (including commercial collaborations) will have access only to my coded (anonymous) data.

YES NO

10. I give permission for blood results and the detection of any other serious illness to be shared with my medical team and GP.

YES NO

11. I give permission for researchers to contact me or my GP in the future to enquire after my physical health and check the status of long term medical conditions such as diabetes, heart disease or cancer.

YES NO

12. I agree that the samples I have given and the information gathered about me can be stored and statistically analysed as coded data put into a computer at the Institute of Psychiatry. To guarantee confidentiality, I agree that researchers external to the study team, including those from commercial collaborators, will only have access to coded data and not to my personal details. I understand I have the right to request, via the study co-ordinator, to review data concerning me, and to have such data modified if inaccurate, or deleted.

YES NO

13. I understand I will not benefit financially if this research leads to the development of a new treatment or medical test but my travel expenses will be reimbursed.

YES NO

14. I request a copy of a newsletter detailing developments in the study and a general summary newsletter at the end of the study.

YES NO

.....	.....	.....
Name of subject	Date	Signature
.....	.....	.....
Name of parent/guardian	Date	Signature
.....	.....	.....
Name of researcher	Date	Signature

Would you like to be sent further information about the project in our newsletter?

YES NO

Contact details for research team: Dr Stefania Bonaccorco, Institute of Psychiatry Tel 0207 848 5480

email: Stefania.Bonaccorso@kcl.ac.uk

APPENDIX 2

CANNABIS EXPERIENCE QUESTIONNAIRE – MODIFIED VERSION (CEQ_{mv})

1. **Have you ever smoked/used cannabis?** Yes No

2. How old were you when you first tried cannabis? _____years

3. **Why did you first try cannabis?** (**You can tick more than one box**)

(a) My friends were using it	Yes	No
(b) My family members were using it	Yes	No
(c) To feel better (to get relief from either physical or psychological discomfort)	Yes	No
(d) Other (please explain) (not for data entry)	Yes	No

---

4. Do you currently use cannabis?

Instructions to researcher: Please consider as current smokers all participants who report usually/customarily smoking cannabis in the last year (incl. patients who have not smoked while inpatient/in prison and patients who report occasional use i.e. once a year).

a. Yes (please answer b) No (please answer c and d)

b. **If yes, why did you continue to use cannabis?** (You can tick more than one box)

(i) I like the effect, it gives me a buzz	Yes	No
(ii) It makes me feel relaxed	Yes	No
(iii) It makes me feel less nervous and anxious	Yes	No
(iv) It makes me feel more sociable	Yes	No
(v) Other (please explain)	Yes	No

---

c. **If no, at what age did you stop? ____ ____**

d. **Please state why you stopped (not for data entry):**

_____

5. Would you like to stop using cannabis one day?

a. Yes No

b. If yes, please explain:

_____

6. Does/did cannabis affect your health in any way?

a. Yes No

If yes, please explain (not for data entry):

_____

7. Does/did cannabis facilitate social situations?

a. Yes No

8. How do/did you <u>mostly</u> use cannabis?

(a) I smoke it in a joint with tobacco

(b) I smoke it in a joint without tobacco

(c) I smoke it using a bong

(d) I eat or drink it

(e) Other (please explain)

_____

9. How often do/did you use cannabis?

(a) Every day

(b) More than once a week

(c) A few times each month

(d) A few times each year

(e) Only once or twice

10. When do/did you <u>mostly</u> use cannabis?

(a) At weekends

(b) During the day

(c) During the evening

(d) During the day and evening

(e) Other (please explain)

_____

11. Do you/did you <u>mostly</u> use cannabis:

(a) Socially (with friends)

(b) On my own

12. On average how much money per week do/did you usually spend on cannabis?

(a) Less than £2.50

(b) £2.50 - £5

(c) £6 - £10

(d) £11 - £15

(e) £16 - £20

(f) Above £20

13. What type of cannabis do/did you <u>mostly</u> use?

(a) Hash (cannabis resin/solid)

(b) Imported herbal cannabis

(c) Home-grown skunk/ Sensimilla

(d) Super skunk

(e) Other (please state)

14. How often have you had these experiences <u>while smoking cannabis</u>? Please rate whether it was a good, bad or neutral experience. If rarely or never, ignore rating (good, bad, neutral) and go to next item.

Fearful

(i) rarely or never

from time to time

sometimes

more often than not

almost always

(ii) Good Bad Neutral

Feel like going crazy/mad

(i) rarely or never

from time to time

sometimes

more often than not

almost always

(ii) Good Bad Neutral

Nervy

(i) rarely or never

from time to time

sometimes

more often than not

almost always

(ii) Good Bad Neutral

Suspicious

(i) rarely or never

from time to time

sometimes

more often than not

almost always

(ii) Good Bad Neutral

Feeling happy

(i) rarely or never

from time to time

sometimes

more often than not

almost always

(ii) Good Bad Neutral

Full of plans/ideas

(i) rarely or never

from time to time

sometimes

more often than not

almost always

(ii) Good Bad Neutral

Hearing voices

(i) rarely or never

from time to time

sometimes

more often than not

almost always

(ii) Good Bad Neutral

Able to understand the world better

(i) rarely or never

from time to time

sometimes

more often than not

almost always

(ii) Good Bad Neutral

Seeing visions

(i) rarely or never

from time to time

sometimes

more often than not

almost always

(ii) Good Bad Neutral

15. How often have you had these experiences <u>after the initial effects of cannabis have worn off</u>? Please rate whether it was a good, bad or neutral experience. If rarely or never, ignore rating (good, bad, neutral) and go to next item.

Not wanting to do anything

(i) rarely or never
from time to time
sometimes
more often than not
almost always

(ii) Good Bad Neutral

Being suspicious without reason

(i) rarely or never
from time to time
sometimes
more often than not
almost always

(ii) Good Bad Neutral

Slowed down thinking

(i) rarely or never
from time to time
sometimes
more often than not
almost always

(ii) Good Bad Neutral

Difficulty in concentrating

(i) rarely or never
from time to time
sometimes
more often than not
almost always

(ii) Good Bad Neutral

Not able to think clearly

(i) rarely or never
from time to time
sometimes
more often than not
almost always

(ii) Good Bad Neutral

16. Life-Time Cannabis History questionnaire.

Instructions to researcher: Please hand this section over to participant for completion. Explain to participant how to complete this part by using (a) as an example: If you were smoking cannabis when you were 15, were smoking 2-3 joints per day on average, you usually smoked hash and you only smoked by yourself.

a. Age range 0-16 (younger to older)

(i) FREQUENCY	**(ii)** QUANTITY	**(iii)** TYPE	**(iv)** SETTING OF USE
	(i) (avg. per day)		
Every day	1 joint	Hash (cannabis resin/solid)	Socially (with friends)
More than once a week	2 or 3 joints		
			On my own
About once a week	4 or more joints	Imported herbal cannabis	
			Both
About once/twice a month	(ii) Mostly shared:	Skunk/ Sensimilla	
A few times each year			
About once a year	YES	Super skunk	
	NO		
I have only used cannabis once or twice		Other	

b. Age range 17-20

(ii) FREQUENCY	**(ii)** QUANTITY (i) (avg. per day)	**(iii)** TYPE	**(iv)** SETTING OF USE
Every day	1 joint	Hash (cannabis resin/solid)	Socially (with friends)
More than once a week	2 or 3 joints		On my own
About once a week	4 or more joints	Imported herbal cannabis	Both
About once/twice a month	(ii) Mostly shared:	Skunk/ Sensimilla	
A few times each year			
About once a year	YES NO	Super skunk	
I have only used cannabis once or twice		Other	

c. Above the age of 21

(iii)FREQUENCY	**(ii)** QUANTITY	**(iii)** TYPE	**(iv)** SETTING OF USE
	(i) (avg. per day)		
Every day	1 joint	Hash	Socially (with
More than once a week		(cannabis resin/solid)	friends)
	2 or 3 joints		On my own
About once a week	4 or more joints	Imported herbal cannabis	
			Both
About once/twice a month	(ii) Mostly shared:	Skunk/ Sensimilla	
A few times each year			
About once a year	YES	Super skunk	
	NO		
I have only used cannabis once or twice		Other	

17. Instructions to researcher: Please give participant prompt sheet and then read out following instruction: 'Please have a look at the list I handed to you and indicate which drugs you use/have used recreationally in the past. Also please state how often you use/have used it, the age at which you first tried the drug(s) and whether you are a past or current user'.
Use a new box for each additional drug and please include tobacco and alcohol where applicable.

a. DRUG: _____

(i) FREQUENCY	**(ii)** AGE	**(iii)** USE	**(iv)** WHEN
Every day		Current	Day
	__ __		
More than once a week		Past	Night
A few times each month			Both day and night
A few times each year			
Only once or twice			

b. DRUG: _____

(i) FREQUENCY	**(ii)** AGE	**(iii)** USE	**(iv)** WHEN
Every day		Current	Day
	__ __		
More than once a week		Past	Night
A few times each month			Both day and night
A few times each year			
Only once or twice			

c. DRUG: _____

(i) FREQUENCY	**(ii)** AGE	**(iii)** USE	**(iv)** WHEN
Every day		Current	Day
	— —		
More than once a week		Past	Night
A few times each month			Both day and night
A few times each year			
Only once or twice			

d. DRUG: _____

(i) FREQUENCY	**(ii)** AGE	**(iii)** USE	**(iv)** WHEN
Every day		Current	Day
	— —		
More than once a week		Past	Night
A few times each month			Both day and night
A few times each year			
Only once or twice			

e. DRUG: _____

(i) FREQUENCY	**(ii)** AGE	**(iii)** USE	**(iv)** WHEN
Every day		Current	Day
	__ __		
More than once a week		Past	Night
A few times each month			Both day and night
A few times each year			
Only once or twice			

f. DRUG: _____

(i) FREQUENCY	**(ii)** AGE	**(iii)** USE	**(iv)** WHEN
Every day		Current	Day
	__ __		
More than once a week		Past	Night
A few times each month			Both day and night
A few times each year			
Only once or twice			

g. DRUG: _____

(i) FREQUENCY	**(ii)** AGE	**(iii)** USE	**(iv)** WHEN
Every day		Current	Day
	— —		
More than once a week		Past	Night
A few times each month			Both day and night
A few times each year			
Only once or twice			

h. DRUG: _____

(i) FREQUENCY	**(ii)** AGE	**(iii)** USE	**(iv)** WHEN
Every day		Current	Day
	— —		
More than once a week		Past	Night
A few times each month			Both day and night
A few times each year			
Only once or twice			

i. DRUG: _____

(i) FREQUENCY	**(ii)** AGE	**(iii)** USE	**(iv)** WHEN
Every day		Current	**D**ay
	— —		
More than once a week		Past	Night
A few times each month			Both day and night
A few times each year			
Only once or twice			

j. DRUG: _____

(i) FREQUENCY	**(ii)** AGE	**(iii)** USE	**(iv)** WHEN
Every day		Current	Day
	— —		
More than once a week		Past	Night
A few times each month			Both day and night
A few times each year			
Only once or twice			

k. DRUG: _____

(i) FREQUENCY	**(ii)** AGE	**(iii)** USE	**(iv)** WHEN
Every day		Current	Day
More than once a week	— —	Past	Night
A few times each month			Both day and night
A few times each year			
Only once or twice			

APPENDIX 3

REASONS FOR USE SCALE (RFUS)

The following questionnaire asks about your reasons for smoking cannabis. Please read each of the reasons on the left. Then, tick only one of the five boxes on each line to show how often you smoke cannabis because of each reason.

		Almost never/ Never	Some of the time	Half of the time	Most of the time	Almost always/ Always
1	To relieve boredom	1	2	3	4	5
2	To make it easier to sleep	1	2	3	4	5
3	To slow down racing thoughts	1	2	3	4	5
4	To be sociable	1	2	3	4	5
5	To relax	1	2	3	4	5
6	To be part of a group	1	2	3	4	5
7	To get high	1	2	3	4	5
8	To decrease suspiciousness / paranoia	1	2	3	4	5
9	To forget your worries	1	2	3	4	5
10	Because its fun	1	2	3	4	5
11	To reduce side effects of medication	1	2	3	4	5
12	Because it makes a social gathering more enjoyable	1	2	3	4	5

		Almost never/ Never	Some of the time	Half of the time	Most of the time	Almost always/ Always
13	To help you talk to others	1	2	3	4	5
14	To get away from the voices	1	2	3	4	5
15	Because you feel more self confident and sure of yourself	1	2	3	4	5
16	Because it helps when you feel nervous	1	2	3	4	5
17	Because its what most of your friends do when you get together	1	2	3	4	5
18	As a way to celebrate	1	2	3	4	5
19	To decrease restlessness	1	2	3	4	5
20	Help me concentrate	1	2	3	4	5
21	Because your friends pressure you to do it	1	2	3	4	5
22	To be liked	1	2	3	4	5
23	So you won't feel left out	1	2	3	4	5
24	It helps when you feel depressed	1	2	3	4	5
25	To feel more motivated	1	2	3	4	5
26	Because it makes you feel good	1	2	3	4	5

APPENDIX 4

READINESS RULER (RR)

Please tick one of the four boxes below to indicate how you feel about your cannabis smoking right now, even if you are not currently smoking.

I never think about smoking less	Sometimes I think about smoking less	I have decided to smoke less	I am already trying to cut back on my smoking
☐	☐	☐	☐

APPENDIX 5

READINESS TO CHANGE QUESTIONNAIRE – TREATMENT VERSION (RCQ-TV)

The following questionnaire is designed to identify how you *personally* feel about your cannabis smoking. Please think about your situation and smoking habits, even if you are not smoking at the moment. Please read each of the statements on the left carefully and then decide whether you agree or disagree with the statement and to what extent. Please tick only one box for each statement that best represents your answer.

		Strongly disagree	**Disagree**	**Unsure**	**Agree**	**Strongly agree**
1	It's a waste of time thinking about my cannabis smoking because I do not have a problem	-2	1	0	1	+2
2	I enjoy my cannabis smoking but sometimes I smoke too much	-2	1	0	1	+2
3	I am trying to stop or cut down on my cannabis smoking	-2	1	0	1	+2
4	There is nothing seriously wrong with my cannabis smoking	-2	1	0	1	+2
5	Sometimes I think I should quit or cut down on my cannabis smoking	-2	1	0	1	+2
6	Anyone can talk about wanting to do something about smoking cannabis but I am actually doing something about it	-2	1	0	1	+2

		Strongly disagree	Disagree	Unsure	Agree	Strongly agree
7	My cannabis smoking is fairly normal	-2	1	0	1	+2
8	My cannabis smoking is a problem sometimes	-2	1	0	1	+2
9	I am actually changing my cannabis smoking right now (either cutting down or quitting)	-2	1	0	1	+2
10	Giving up or smoking less cannabis would be pointless for me	-2	1	0	1	+2
11	I am weighing up the advantages and disadvantages of my present cannabis smoking	-2	1	0	1	+2
12	I have started to carry out a plan to cut down or quit smoking cannabis	-2	1	0	1	+2
13	There is nothing I really need to change about my cannabis smoking	-2	1	0	1	+2
14	Sometimes I wonder if my cannabis smoking is out of control	-2	1	0	1	+2
15	I am actively working on my cannabis smoking	-2	1	0	1	+2